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Review Article

Global Distribution, Public Health and Clinical Impact of the Protozoan Pathogen *Cryptosporidium*

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Cryptosporidium spp. are coccidians, oocysts-forming apicomplexan protozoa, which complete their life cycle both in humans and animals, through zoonotic and anthroponotic transmission, causing cryptosporidiosis. The global burden of this disease is still underascertained, due to a conundrum transmission modality, only partially unveiled, and on a plethora of detection systems still inadequate or only partially applied for worldwide surveillance. In children, cryptosporidiosis encumber is even less recorded and often misidentified due to physiological reasons such as early-age unpaired immunological response. Furthermore, malnutrition in underdeveloped countries or clinical underestimation of protozoan etiology in developed countries contribute to the underestimation of the worldwide burden. Principal key indicators of the parasite distribution were associated to environmental (e.g., geographic and temporal clusters, etc.) and host determinants of the infection (e.g., age, immunological status, travels, community behaviours). The distribution was geographically mapped to provide an updated picture of the global parasite ecosystems. The present paper aims to provide, by a critical analysis of existing literature, a link between observational epidemiological records and new insights on public health, and diagnostic and clinical impact of cryptosporidiosis.

1. Introduction

1.1. The Cryptosporidium Parasite: General Description. Infections of the human gastrointestinal tract with enteric pathogens are among the leading causes of disease, suffering, and death worldwide. Enteric pathogens are ingested with contaminated water and food and pass through the entire gastrointestinal tract. After establishment in a host, the infection spread to new hosts by a subsequent shedding. The most important and prevalent infections of the small intestine are caused by diarrheagenic *Escherichia coli*, particularly enterotoxigenic and enteropathogenic *E. coli*, Rotavirus, *Giardia lamblia*, and *Cryptosporidium parvum* [1–3]. Particularly, more than 58 million cases of diarrhea detected per year in children are associated to intestinal protozoa infections with high morbidity and mortality infection rates [4]. *Cryptosporidium* spp. are oocysts-forming apicomplexan protozoa. Following ingestion, the oocyst excystation, releases sporozoites which invade enterocytes. The excysted parasites undergo asexual (*merogony*) and sexual multiplication (*gametogony*) producing macrogametocytes and microgametocytes. Upon fertilization of the macrogametocytes by microgametes a zygotes is developed which sporulates (*sporogony*), generating *thin-walled* oocysts, involved in autoinfection and *thick-walled* oocysts excreted from the host (Figure 1). Once released in the environment, the parasite may cause enteric infection (cryptosporidiosis) both in humans and animals, mainly transmitted via the fecal-oral route through a zoonotic or *anthroponotic* modality or via contaminated water or food (Figure 2). In humans the disease results in sickness and severe diarrhea and can be life threatening in the very young, elderly and in immunosuppressed individuals, particularly those with HIV infection [5]. Contamination of drinking water by *Cryptosporidium* can result in major waterborne outbreaks of cryptosporidiosis [6]; additionally the *Cryptosporidium* is now increasingly considered an important foodborne pathogen [7, 8] causing a disease of socioeconomic significance worldwide. Three features of *Cryptosporidium* spp. ensure a high level of environmental contamination and

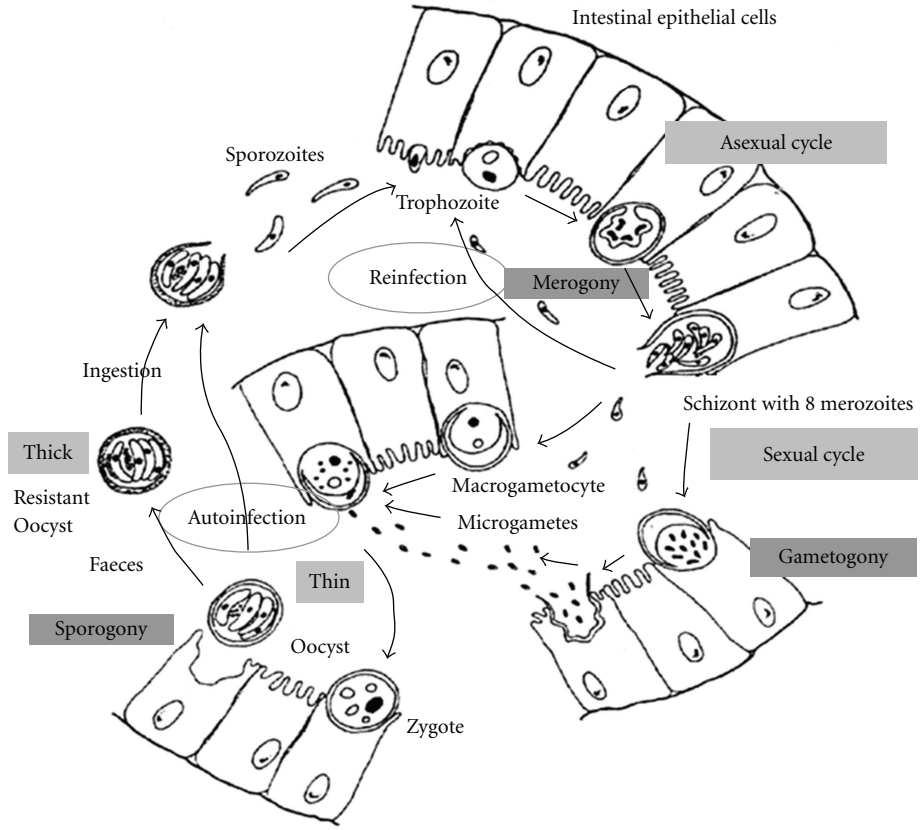


Figure 1: *Life cycle of Cryptosporidium in the enterocyte.* Following oocyst ingestion by a host, and excystation, the sporozoites are released and parasitize epithelial cells of the gastrointestinal tract. In these cells, the parasites undergo asexual multiplication (*schizogony* or *merogony*) and then sexual multiplication (*gametogony*), producing microgamonts and macrogamonts. Upon fertilization of the macrogamonts by the microgametes, oocysts develop and sporulate in the infected host. Two different types of oocysts are produced: the *thick-walled*, which is commonly excreted by the host, after *sporogony*, and the *thin-walled* oocyst, which is primarily involved in autoinfection. Putignani and Menchella, 2010.

increase the likelihood of waterborne transmission. Firstly, they are responsible for disease in a broad range of hosts including man [9, 10], have a low-infectious dose (10–30 oocysts) enhancing the possibility of infection also in healthy immunocompetent people [11, 12], which may shed 10^8-10^9 oocysts in a single bowel movement and excrete oocysts for up to 50 days after cessation of diarrhea [13, 14]; secondly, their transmissive stages (oocysts) are small in size and environmentally robust [15, 16] and thirdly, they are insensitive to the normal disinfectants commonly used in the water industry [17, 18].

1.2. Cryptosporidium Species and Human Infection. Since the genus *Cryptosporidium* was established for *Cryptosporidium muris* by Tyzzer in 1907, 37 species names have been introduced. However, after redescription and confirmation, currently 21 names are associated with individual species [19] and 16 species are actually regarded as valid on the basis of different oocyst morphology, site of infection, vertebrate class specificity, and genetic differences: *C. muris* in rodents; *Cryptosporidium andersoni* and *Cryptosporidium bovis* in cattle and sheep; *Cryptosporidium suis* in pigs; *C. parvum* in cattle, humans, and other mammals; *Cryptosporidium meleagridis* in birds and humans; *Cryptosporidium hominis* in humans; *Cryptosporidium baileyi* and *Cryptosporidium galli* in birds; *Cryptosporidium serpentis* and *Cryptosporidium saurophilum* in snakes and lizards; *Cryptosporidium molnari* and *Cryptosporidium scophthalmi* in fish; *Cryptosporidium wrairi* in guinea pigs; *Cryptosporidium felis* in cats; *Cryptosporidium canis* in dogs [20]. The majority of these have a dominant host, but they are accidentally found in possibly unusual hosts. Remarkably, *Cryptosporidium* parasites are not related to other coccidians and the major recognised species in *Cryptosporidium* separate into two broad groups, with *C. muris* and *C. serpentis* forming one group and *C. parvum*, *C. felis*, *C. wrairi*, *C. meleagridis*, and *C. baileyi* forming a second broad group [21]. The accurate identification and characterisation of *Cryptosporidium* species and population variants are now central in the new taxonomic classification of *Cryptosporidium* species and in the categorization of genotypes or subtypes [20]. The picture that is emerging as a result of molecular studies clearly indicates that the species level taxonomy of the genus does not reflects the current molecular phylogenetic analyses or epidemiological data, which show high inter- and

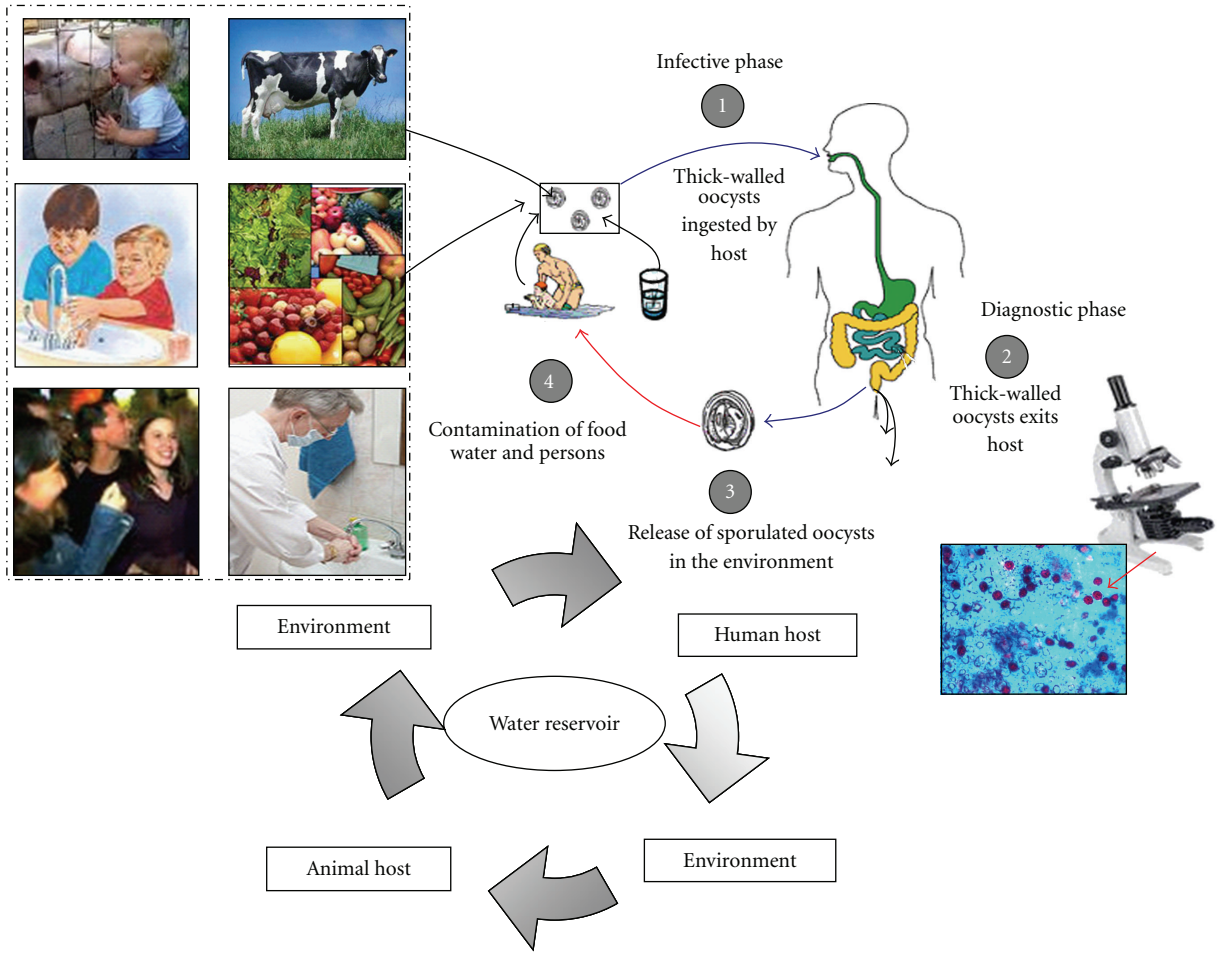


Figure 2: *Description of transmission modes of Cryptosporidium.* Following ingestion (and possibly inhalation) by a suitable host (e.g., human host), excystation occurs (*infective stage*, (1)). The released sporozoites invade epithelial cells of the gastrointestinal tract or other tissues, complete their cycle producing oocysts which exit host (*diagnostic stage*, (2)) and are released in the environment (3). Transmission of *Cryptosporidium* mainly occurs by ingestion of contaminated water (e.g., surface, drinking or recreational water), food sources (e.g., chicken salad, fruits, vegetables) or by person-to-person contact (community and hospital infections) (4). Zoonotic transmission of *C. parvum* occurs through exposure to infected animals (person-to-animal contact) or exposure to water (*reservoir*) contaminated by feces of infected animals (4). Putignani and Menchella, 2010.

intraspecific variation, and warrants reappraisal [21]. The vast majority of human cases of cryptosporidiosis worldwide are mainly caused by two species, *C. parvum* and *C. hominis* [21]. However other species, including *C. felis* [22, 23], *C. meleagridis* [23, 24], *C. canis* [23, 25], *C. suis* [23], *C. muris* [26], and more rarely *C. baileyi* [27] can infect humans too, especially children under the age of 5 years and immunocompromised individuals [28]. All *Cryptosporidium* species are transmitted in the various hosts by ingestion and inhalation of oocysts, irrespective of the species types. However, the clinical and epidemiological significance of various *Cryptosporidium* species and subtypes in humans is not yet clear. Results of recent genotyping studies nevertheless support the theory that *C. hominis* and *C. parvum* behave differently in humans especially with reference to the specificity of the clinical presentation. In *C. hominis* cases, nongastrointestinal symptoms (e.g., joint pain, eye pain, headache, dizziness and fatigue) are seen more often than in cases of *C. parvum*. Furthermore in young children, infections with *C. hominis* and, if symptomatic, *C. parvum*, are often heavy associated with fecal lactoferrin and growth shortfalls. *C. hominis* appears to stimulate inflammation irrespective of age; this raises important questions regarding how it may specifically induce greater proinflammatory response [29].

1.3. Transmission Modes and Risk Factors

1.3.1. Impact of Water Livestock on Transmission. Waterborne contamination is a growing concern causing widespread disease outbreaks. Factors that have contributed to the emergence of cryptosporidiosis in animals include increased environmental contamination and trends in livestock production. In humans the zoonotic nature of infection, along with increased numbers of at-risk population have contributed to the rate intensification of the disease [30]. Risk factors for

Table 1: Factors that affect prevalence and adequate surveillance of cryptosporidiosis.

Epidemiological indexes
Population age
Gender
Individual immunological status
Geographical distribution and ethnic group
Human activities
Hygienic and diet practices
Rural and urban settings
Human waste contamination
Livestock pollution
Water treatment systems; food preparation styles and procedures
Travels, immigration
Environmental and social affecting factors
Animal pollution
Famine, malnutrition, dehydration
Geography, international adoptions
Calamities (typhoons, local wars, floods, etc)
Climate variation, pollution, deforestation and seasonal rains
Under-ascertainment factors in surveillance
Improper sampling of contaminated water systems and food
Difficulty to identify the likely source of infection
Misidentification of outbreak sources
Multiple protozoan coinfections
Under-ascertainment factors in clinics and diagnosis
Poor or diversified symptom presentations and low clinician's sensitivity to consider protozoa as agents of gastrointestinal infections
Limited inclusion of protozoan searching in operational diagnostic workflows
Self-limiting infection course in immunocompetent adults and children
Low inclusion of advanced molecular tools for routine diagnosis

waterborne infections are deduced primarily from outbreak surveillance data. However, in the USA, only a fraction of the estimated water-related outbreaks are reported through passive surveillance [31]. While the outbreak epidemiology due to cryptosporidiosis is still a matter of concern, despite objective definition and identification of outbreak [32], the epidemiology of sporadic (non-outbreak-related) cases is largely unknown. Few papers have reported studies using the Geographical Information System (GIS) methods to map the locations of residences of sporadic cases or to assess ecosystems of cryptosporidiosis [33–36]. In the last few years a plethora of literature has been focusing on the description of advanced molecular markers and technologies [37–41], population structures [42–44], genetic variation of the parasite [45, 46], and linkage to its complex epidemiology [10, 47–50].

1.3.2. Impact of Climate and Weather on Transmission. A seasonal incidence of infection is sometimes present, possibly corresponding to rainfall peaks, increased pollution from farm waste, or calving and lambing activities [51, 52] (Table 1). Pivotal works have thoroughly investigated the seasonality of cryptosporidiosis also for children, showing highest prevalence from October to March. Such pattern may suggest a possible relationship with child care centre attendance in Europe [53], or provide correlation between seasonality and endemicity in Africa [54]. Recently, a meta-analysis has examined the seasonal patterns of cryptosporidiosis, with relation to precipitation and temperature fluctuations worldwide [55], according to the geographical *Köppen Climate Classification* [56]. Outcome data were linked to monthly ambient temperature and precipitation for each location and, for the Sub-Saharan Africa, to the *Normalized Difference Vegetation Index*, a remote sensing measure for the combined effects of temperature and precipitation on vegetation and cryptosporidiosis. Strong seasonal drivers for cryptosporidiosis showed precipitation in moist tropical locations and temperature in mid-latitude and temperate climates [55]. While climatic conditions typically define a pathogen habitat area, meteorological factors affect timing and intensity of seasonal outbreaks. Therefore, seasonality and meteorological forecasts can represent a key indicator and tool, respectively, to plan prevention programs for waterborne cryptosporidiosis (Table 1).

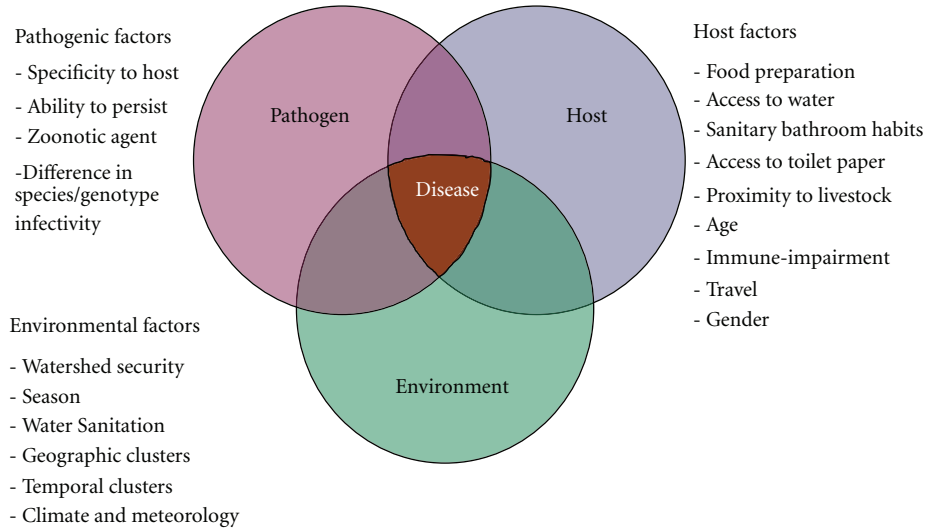


Figure 3: *Venn Diagram of factors leading to Cryptosporidium infection.* Parasite, host and environmental indexes acting as key factors for the global burden of cryptosporidiosis. For details see Table 1. Putignani and Menchella, 2010.

1.4. Cryptosporidiosis a "Neglected Disease" and a Poverty Index. In developing countries the impact of protozoan pathogens represents a major cause of gastrointestinal illnesses and is becoming of growing impact, also because new epidemiological markers and indicators of infection are allowing researchers and clinicians to strengthen surveillance programs and diagnostic procedures [36, 44, 57]. However, a large proportion of diarrhoeal illnesses in these countries, especially in children, are still ascribed to an unknown etiology, often because the only available detection methods, such as microscopy and culture used in many areas, have low sensitivity. Particularly, *Cryptosporidium* and *Giardia* are still major causes of diarrhoeal diseases of humans worldwide, and are included in the *World Health Organisation*'s *Neglected Diseases Initiative* [58, 59]. The neglected tropical diseases are often indicators of poverty and disadvantage. Those most affected are the poorest populations often living in remote, rural areas, urban slums, conflict and natural disaster zones, where aggravate conditions are conducive to the spread of these diseases (Table 1). *Cryptosporidium* accounts for up to 20% of all cases of childhood diarrhea in developing countries, and is a potentially fatal complication of AIDS [30] and often, in early childhood, is often associated with poor cognitive function and failure to thrive [60].

1.5. Clinical Symptoms As Patognomic Evidence. Variation in symptoms may represent and additional key indicator to set up specific diagnostic workflows for *Cryptosporidium* detection and to infer correlation between infecting species/subtypes and epidemiology (Table 1) (Figure 3). In the last few years, in low-income countries, an enhanced attention has been directed to the observation of symptom variation, which may provide a successful index for wholesale effective surveillance programs [50, 61]. A recent extensive study was performed in Bangladesh on 3646 case patients, who presented with diarrhea [61]. The study assessed the proportion of diarrhea cases attributable to *C. hominis*, *C. parvum*, *Entamoeba histolytica*, and *G. lamblia*. *Cryptosporidium* species and *E. histolytica* were more prevalent in patients with acute diarrhea, all ages and, specifically, those from 0 to12 months of age. Remarkably, patients with diarrhea and cryptosporidiosis were less likely to have abdominal pain; patients with amebiasis were more likely to have visible blood in stool; patients with giardiasis were more likely to be dehydrated, compared with control subjects [61]. Recently, clinical symptoms such as abdominal pain and/or diarrhoea were selected as key indicators of *Cryptosporidium* and *Giardia* infections in patients in Belgium (Table 2) [62].

1.6. Epidemiology of Cryptosporidium Species. *C. hominis* and *C. parvum* are the major causing agents of human cryptosporidiosis both in immunocompetent and in immunocompromised individuals but their prevalence varies in different regions of the world [49]. Macroepidemiological analyses showed that *C. hominis* is more prevalent in North and South America, Australia, and Africa, whereas *C. parvum* causes more human infections in Europe, especially in the UK [49]. Particularly, *C. meleagridis* can be confirmed as an emerging human pathogen, being responsible for 1% of all infections in England [49] and about 10% in Perù, where its prevalence is as high as for *C. parvum* [50]. A recent important long-term typing overview reported the epidemiology of human cryptosporidiosis in the UK (England and Wales) by analysing 8,000 *Cryptosporidium* isolates which were submitted for typing from 2000 to 2003 [63] (Table 2). The majority were either *C. parvum* or *C. hominis*. Six other known *Cryptosporidium* species or genotypes were found: *C. meleagridis*, *C. felis*, *C. canis*, and the *Cryptosporidium* cervine [64], horse and skunk [65] genotypes. This study showed that epidemiology differed among infecting species (Figure 3). *C. parvum* cases were younger, although *C. hominis* was more prevalent in infants

Table 2: Worldwide distribution of principal sporadic cases and surveillance data reported in the last decade (1998–2008): case characteristics.

Samples (surveillance study or sporadic cases)	Country	Age (human cases)	Technique/genotyping tool	Species/genotypes/subgenotypes[1]	Reference
Human stools	India	Children	18S rRNA, SSU, COWP, Cpgp40/15, TRAP-C1-based PCR	*C. hominis* (Ia, Id, Ie, Ib), *C. parvum* (Ic), *C. felis*	[36]
Environmental (water)	China	—	18S rRNA PCR-RFLP and sequence analyses; GP60	*C. hominis* (IbA19G2, IbA20G2, and IbA21G2), Ia, Id, Ie (IeA12G3T3), If (IfA22G1) *C. meleagridis*, *C. baileyi*, *C. parvum*, *C. suis*, *C. muris*, rat genotype, avian genotype 3	[41]
Human stools	Perù	Children	GP60	*C. hominis* (Ia, Ib, Id, Ie, Id), *C. parvum* (IIc), *C. meleagridis*, *C. canis*, *C. felis*	[50]
Human stools	Ireland	Adults and children	18S rRNA and COWP PCR-RFLP; GP60	*C. hominis* (IbA10G2), *C. parvum* (IIaA18G3R1)	[51]
Human stools	Belgium	Adults and children	70-kDa heat shock protein, 60-kDa glycoprotein (GP60)	*C. hominis* (IbA10G2, IbA9G3) *C. parvum* (IIaA15G2R1, IIcA5G3a, IIdA16G1 IIaA15G2R1)	[62]
Human stools	UK	Adults and children	COWPand small sub-unit (SSU) rRNAgene PCR-RFLP	*C. parvum, C. hominis*, *C. meleagridis*, *C. felis*, *C. canis*, *Cryptosporidium* cervine, horse, skunk genotypes	[63]
Human stools	Haiti	Adults and children	18S rRNAPCR-RFLP	*C. hominis*, *C. parvum, C. felis*	[69]
Human stools	Perù	Adults	GP60	*C. hominis* (Ia, Ib, Id, Ie) *C. canis*, *C. felis*, *C. parvum*, *C. meleagridis*	[74]
Human and animal stools	Portugal	Adults and children	GP60	*C. hominis* (Ib, If), *C. parvum* (IIa, IIb, IIc and IId)	[78]
Environmental (water)	France	—	IMS-IFA[2], 18S rRNA PCR-RFLP	*C. hominis*, *C. parvum*	[96]
Animal stools	Ireland	Neonatal calves	GP60	*C. parvum* (IIaA18G3R1), *C. bovis*, *Cryptosporidium* deer-like genotype	[101]
Environmental (water)	Portugal	—	IMS-IFA[1], PCR	*C. hominis* (IdA15) *C. parvum* (IIaA15G2R1, IIaA16G2R1, IIdA17G1)	[103]
Animal and human stools	Portugal	Adults and children	GP60	*C. hominis*, *C. parvum*, *C. felis*, *C. meleagridis*	[104]
Human stools	MI (USA)	Adults and children	18S rRNA and COWPPCR-RFLP; GP60	*C. hominis*, *C. parvum* (cervine genotype, cervine genotype variant, human genotype W17)	[148]
Animal and human stools	Iran	Children and one adult	18S rRNA PCR-RFLP	*C. parvum*, *C. hominis* (anthroponotic and zoonotic genotype)	[164]
Animal stools	China	Neonatal calves	70-kDa heat shock protein; 18S rRNA, actin-based PCR	*C. andersoni*, *C. ryanae*	[165]
Animal stools	India	Neonatal calves	18S rRNA PCR-RFLP	*C. parvum*, *C. hominis*	[206]
Human stools	UK	Adults and children	SSCP-based analysis of the 18S rRNA SSU and ITS-2 spacer	*C. parvum* (types 1 and 2)	[208]
Human stools	UK	Adults	GP60	*C. hominis* (IbA10G2)	[209]
Human stools	Kenya, Malawi, Brazil, Vietnam, UK	Adults and children	18S rRNA PCR-RFLP	*C. parvum* (human genotype), *C. parvum* (bovine genotype), *C. meleagridis*, *C. muris*	[222]

Table 2: Continued.

Samples (surveillance study or sporadic cases)	Country	Age (human cases)	Technique/genotyping tool	Species/genotypes/subgenotypes[1]	Reference
Human stools	Switzerland, Kenya, USA	Adults and children	18S rRNA; HSP-70; acetyl coenzyme A synthetase	*C. parvum* ("human" genotype, "cattle" genotype), *C. felis*, *C. meleagridis*	[223]
Human stools	Spain	Adults and children	18S rRNA-, COWP-based PCR-RFLP	*C. hominis*, C. *parvum*, *C. meleagridis*, *C. felis*	[224]
Human stools	Equatorial Guinea	Adults and children	COWP-based PCR-RFLP	*C. parvum*, *C. hominis*, *C. meleagridis*	[232]
Human and animal stools	Thailand	Adults	18S rRNA PCR	*C. parvum*	[239]
Human stools	Perù	Adults and children	18S rRNA-based PCR-RFLP	*C. hominis*, *C. meleagridis*, *C. parvum*, *C. canis*, *C. felis*, *Cryptosporidium* (pig genotype)	[240]
Human stools	Poland	Adults and children	COWP and β-tubulin-based PCR	*C. hominis*, *C. parvum*, *C. meleagridis*,	[254]
Human stools	Madagascar	Children	GP60	*C. hominis* (Ia, Id, Ie), *C. parvum* (IIc)	[275]

[1]When available, reported subgenotypes are the most common detected.
[2]IMS-IFA, immunomagnetic separation followed by immunofluorescence assay: Method 1623 of the *USA Environmental Protection Agency* (USEPA).

under one year and in females aged 15 to 44 years. Spring peaks were due to *C. parvum,* while *C. hominis* was more prevalent during the late Summer and early Autumn as well as in patients reporting recent travel abroad [63] (Table 1) (Figure 3) (Table 2). *C. parvum* and *C. hominis* are two species responsible for most human cases of cryptosporidiosis. The relationship between the global population structure of these species and the host population arrangement was thoroughly investigated by the study of Tanriverdi et al., 2008 [66], in which a series of worldwide *C. parvum* and *C. hominis* isolates were genotyped. Geographical partitions or patterns for both parasite species were observed among the countries (Uganda, Serbia, Turkey, Israel, UK, USA, and New Zealand), possibly because of different prevailing ecological determinants of transmission [66]. Rather than conforming to a strict paradigm of either a clonal or a panmictic population structure [43], these data seem to suggest a flexible reproductive strategy characterized by the cooccurrence of both propagation patterns.

A predominance of *C. hominis* was observed in persons in developing countries, such as pediatric populations from Perù [26, 50], Malawi [67], Kenya [68], India [36], Haiti [69], and Brazil [70], children and elderly persons from South Africa [71], and hospitalized HIV-infected children from South Africa [72] and Uganda [73]. A comparatively large proportion of participants infected with *C. meleagridis* was observed in a wide community in Haiti [69], a finding that was also reported at a high frequency in HIV-infected adults in Perù [74]. This species has been reported, even if rarely, by other studies regarding either children or adults with or without HIV infection from other geographical places as Portugal [75], India [36, 57], Taiwan [76], or Iran [77].

Environmental isolates of *Cryptosporidium* from China were thoroughly investigated in the study of Feng et al., 2009 (Table 2) [41]. Interestingly, the predominant species was *C. hominis* followed by *C. meleagridis*. The other *Cryptosporidium* species/genotypes identified included *C. baileyi*, *C. parvum*, *C. suis*, *C. muris*, rat genotype, avian genotype 3, and a novel genotype. The Ib identified subtypes (Table 2) [41], were very different from the subtypes IbA9G3 and IbA10G2 commonly found in other areas of the world. The IbA9G3 is usually observed in humans in Kenya, India, and Australia, and IbA10G2 is commonly seen in South Africa, Perù, USA, Canada, Australia, and European countries, as France, UK, Portugal, Spain and Ireland [50, 68, 72, 78–84]; IbA10G2 is responsible for more than half of the waterborne outbreaks in USA, and Canada [85, 86]. Likewise, the IeA12G3T3 was different from the most common IeA11G3T3 subtype, although observed also in Louisiana, Australia, and Jamaica [79, 87, 88] (Table 2). Also the IfA20G1 and IfA22G1 subtypes were detected, as previously in children in South Africa [72], occasionally in HIV-positive adults in Portugal [78] and in India [89], but not in most other studies, supporting the presence of unique transmission of *C. hominis* in China (Table 2).

In spite of the availability of substantial sequence data obtained by reliable typing tools (e.g., COWP, TRAP C-1, GP60) there is still no comprehensive analysis of the genetic richness, and diversity within *C. hominis* and *C. parvum* [90]. The worldwide literature produced so far highlights the need to pursue on detailed molecular epidemiological studies (e.g., GP60), especially in "neglected" geographical regions and from a wide range of hosts species. Indeed researchers have to address the key question if the low diversity associated to the substantial richness of the GP60 locus is due to the genetics of the organism or to a lack of data from countries with potential endemic transmissions (Africa, South east, China, and India subcontinents) [90]. High-throughput technologies ("genome sequence surveys") and advanced bioinformatic platforms

(http://cryptodb.org/cryptodb/) may allow unprecedented comparative studies of *Cryptosporidium* isolates and overcome the limits of incomplete global epidemiological data.

1.7. Diagnostic Pitfalls: The Case of a Developed Country. An interesting case-control study [91], performed in Lower Saxony (Germany), during 2001 to 2005, reported 744 cases of cryptosporidiosis detected by the Governmental Institute of Public Health. The study demonstrated that a broad and improved diagnostic activity in reference laboratories was able to better describe cryptosporidiosis, reflecting the real occurrence of this infection, often underestimated. The yearly incidence rate of 1.9 notified cases per 100 000 population within Lower Saxony exceeded the German mean incidence rate of 1.5. In several neighbouring districts there was a striking heterogeneity of regional incidences. However, highest rates of notification were associated with one particular laboratory where all stool samples, submitted for routine microbiological diagnosis, were screened for *C. parvum*. Diagnostic work was done by valid, specific, CE-certified procedures. The inferred conclusion was that the increased regional incidence rate was caused by the extensive diagnostic activity of this laboratory, presuming an underestimation in other regions [91]. These data seem to suggest that, even in high-income countries, routine diagnostic protocols should be thoroughly integrated by highly advanced identification workflows.

1.8. Aims of the Review. This review aims to discuss the updated global distribution of cryptosporidiosis, focusing on the main records reported for sporadic cases and outbreaks in the last decade and exploiting spatial and temporal determinants of infection particularly for low-income countries. With this intent, key indicators were critically considered to describe dynamics of transmission linked to the principal reservoirs of environmental infection (e.g., water, food) but also to the main host factors (e.g., age, travel, immunostatus) (Table 1) (Figure 3).

The principal cryptosporidiosis ecosystems, linked to outbreak and sporadic human cases, were geographically mapped worldwide (Figure 4) and origins of infection were categorised as *Waterborne* (Section 3), *Foodborne* (Section 4), *Travelers*' (Section 5), and HIV-related disease (Section 6). Cryptosporidiosis in children was separately approached, according to multivariate and specific exposure factors acting in this life age (Section 7). The set of reviewed data (outbreak and sporadic human cases, environmental and veterinary surveillance reports) was correlated, in each Section, to the geographical setting (continent) and subsetting (country) (Figure 4, Figure 5).

2. Study Approach

International surveillance networks and suites of free and open-source for epidemiology control or open-access peer-reviewed journals about infectious diseases surveillance prevention and control in Europe, Canada, USA, and Australia were exploited for our analysis (Table 3).

The MEDLINE database (http://www.ncbi.nlm.nih.gov/sites/entrez) was searched for the following terms: *Cryptosporidium*, cryptosporidiosis, water- and foodborne outbreak, travelers' cryptosporidiosis, HIV cryptosporidiosis, children cryptosporidiosis. More than 400 papers were found to be eligible after reading the full text and/or abstract. Of these potentially adequate articles, 300 fulfilled the inclusion criteria: (i) presence of rate data of cryptosporidiosis within the last decade; (ii) presence of geographical distribution and transmission data for relevant sporadic cases and outbreak occurred in the last decade; (iii) observation of potential environmental factors affecting and/or worsening the occurrence of parasite transmission (Table 1) (Figure 3).

3. Cryptosporidiosis a "Waterborne Disease"

3.1. Outbreaks Associated to Protozoan Parasites. *C. parvum* accounts for the majority of 325 water-associated outbreaks of parasitic protozoan diseases recently worldwide reported (165 out of 325, 50.8%), immediately followed by *Giardia duodenalis* (132 out of 325, 40.6%) and afterwards by *E. histolytica* (9 out of 325, 2.8%), *Cyclospora cayetanensis* (6 out of 325, 1.8%), and in the least by *Toxoplasma gondii* and *Isospora belli* (3 out of 325, 0.9% each), *Blastocystis hominis* (2 out of 325, 0.6%) and *Balantidium coli*, the microsporidia, *Acanthamoeba* and *Naegleria fowleri* (1 out of 325, 0.3% each) [6].

Out of the 71 *Cryptosporidium*-linked outbreaks described in the last decade, 40 (56.3%) appear to be correlated to waterborne diseases, with a distribution almost constant throughout the years, marked by picks in 2000, 2001, 2002, and 2007. Geographically, the outbreaks seem to be concentrated in the USA, Canada, Australia and in Europe, especially in the UK and Ireland and appear to affect both adults and children (Table 4) (Figure 4). Worldwide environmental and veterinary surveillance data reveal the presence of *Cryptosporidium* spp. in the entire water-treatment system, which represents an unacceptable health risk, particularly in sensitive (pregnant women, children) and immunocompromised populations (HIV-positive and transplanted patients). Such evidence suggests that focus ought to be placed on prevention of human and animal waste contamination especially in authorized recreational waters, and in a few cases also in well-maintained community swimming pools treated by supplemental disinfection treatment. Remarkably, cryptosporidiosis is nowadays the most frequently reported gastrointestinal illness in outbreaks associated with treated (disinfected) recreational water venues in USA [92]. However, microbiological surveillance should be also directed to other fresh waters, affected by occasional peaks of contamination, owing to heavly rainfall going through fields to lakes, or by high-contamination events that might occur upstream from the sampling river sites irrigation. In USA, where large episodes of cryptosporidiosis are detected, public water treatments should steadily adhere to USA Environmental Protection Agency (USEPA) regulations to improve water quality, aquatic venue design, usage, and maintenance and to update the Center for diseases control and prevention (CDC)

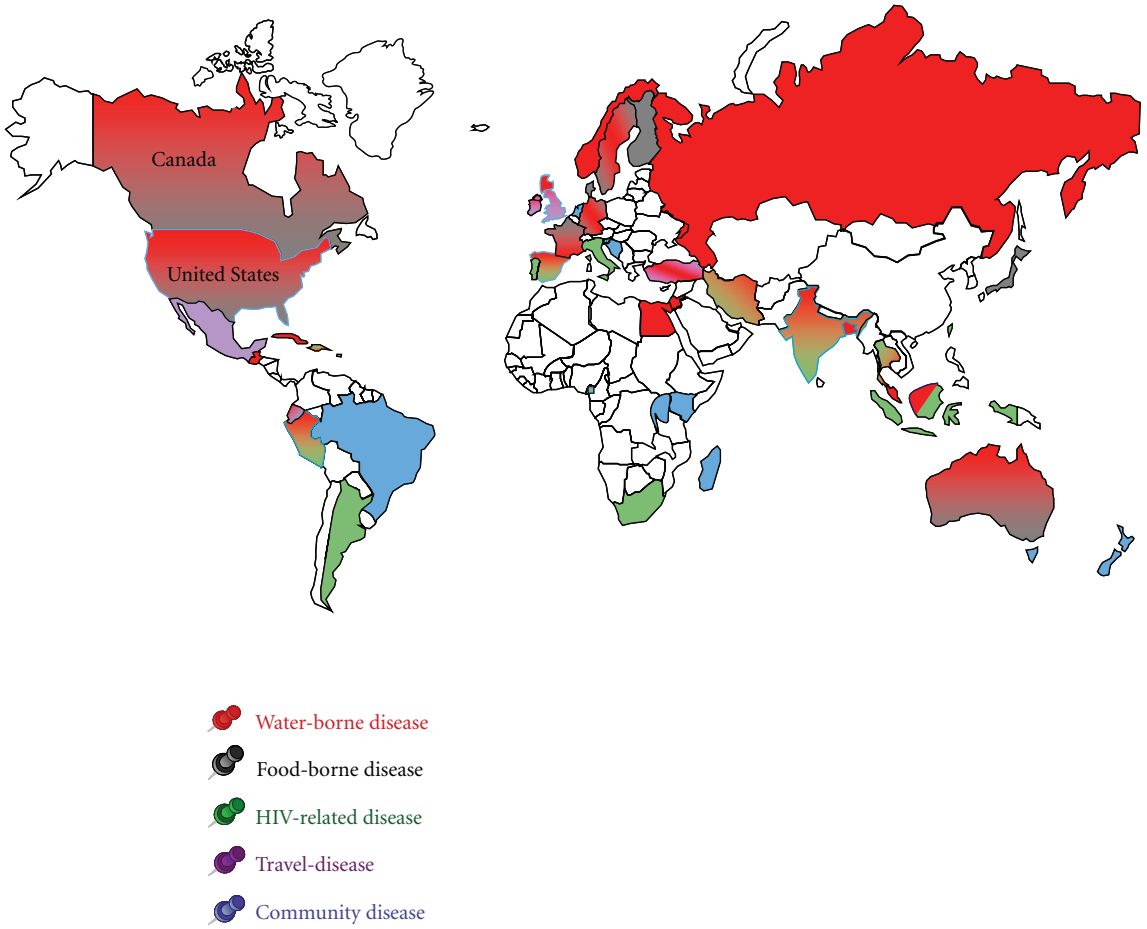


Figure 4: *Geography of worldwide occurrence of human cryptosporidiosis outbreaks and sporadic cases.* A color-coded distribution of the main cases of cryptosporidosis reported in the literature during the last decade (1998–2008) for the entire population (adults and children) is here represented. Waterborne and foodborne diseases are represented by red and grey color, respectively. Spreading of the infection due to HIV immunological impairment is represented by green and travel-related disease by pink color. When not applicable the definition of waterborne and foodborne disease, the term community disease has been applied to person-to-person contacts and represented by a pale blue color. For countries characterised by two or three coexisting transmission modes, a double color-filling effect plus thick border lines have been used, consistently with the above reported code. Putignani and Menchella, 2010.

surveillance programs with periodical reports on etiologic agents, failures of water-treatment systems, and deficiencies associated with outbreak management [93] (Table 3). In developed countries, the detection of *Cryptosporidium* and *Giardia* should be an integral part of the quality system in the water industry and multidisciplinary approaches among public health professionals (epidemiologists, clinicians and parasitologists) should be routinely included to establish priorities in public health prevention programs and to design appropriate operational workflows for both detection and diagnosis. In developing countries the potential of infection is enhanced by the absence of sanitary and parasitological drinking water monitoring. Moreover the burden of the infection is surely underestimated for the small number of appropriate surveillance programs and for the absence of suitable diagnostic algorithms.

3.2. Waterborne Cryptosporidiosis in Europe. Recently, in Europe, the circulation of *Cryptosporidium* spp. populations has been thoroughly investigated because of the improved surveillance and diagnosis of both sporadic cases and outbreaks of cryptosporidiosis (Table 4). From a waterborne outbreak of diarrhea in France, the 91% of the isolates of the parasite were characterised as *C. hominis* type Ib [86], consistently with the current idea that Ib is the predominant allele associated with waterborne cryptosporidiosis worldwide [79, 81].

Earlier evidence had suggested that accidental ingestion of natural waters while bathing carries a risk of infection by waterborne protozoa both in UK and USA [94, 95]. In order to evaluate this risk in France, a one-year prospective study on recreational lakes and river sites located near Paris, chosen for frequent bathing and boating, was undertaken (Table 2) [96]. *Giardia* cysts and *Cryptosporidium* oocysts were detected in the recreational lakes with occasional peaks and in the river sites throughout all the year. Genetic characterization of *Cryptosporidium* revealed the presence of both *C. hominis* and *C. parvum* species (Table 2). Based on

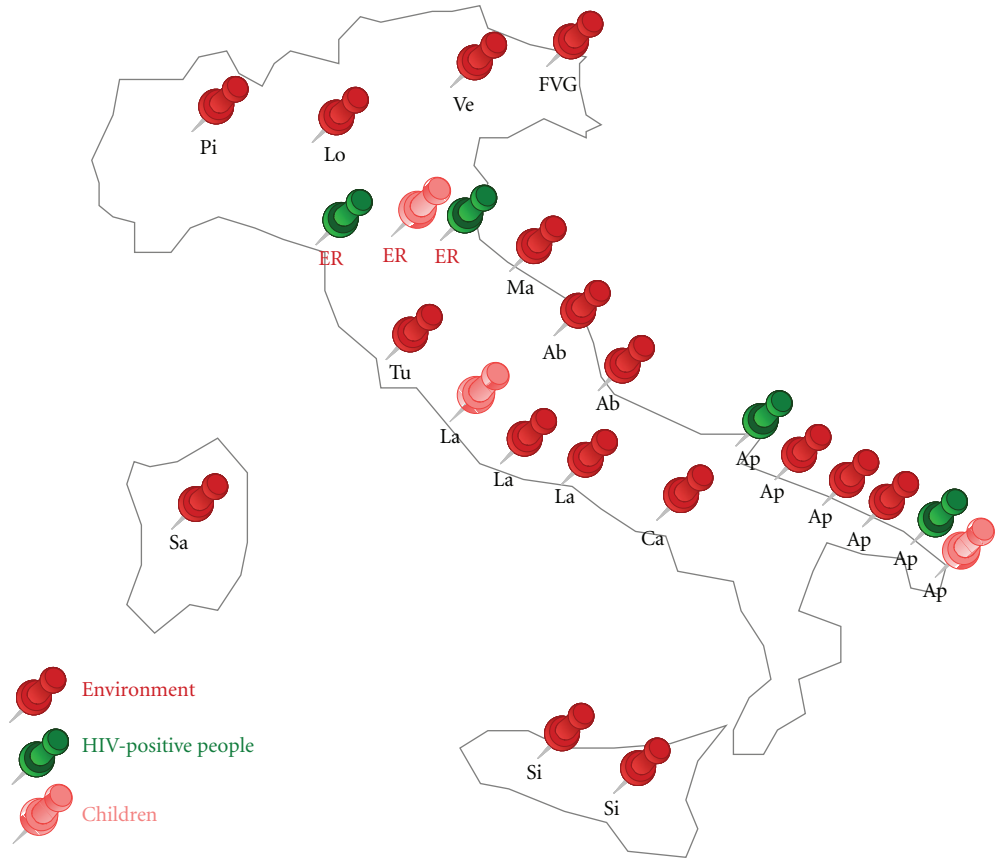


Figure 5: *Geographical distribution of Italian studies on Cryptosporidium surveillance.* A map of the principal surveillance studies performed on environmental and human samples is here reported by using the following color codes: red for environmental samples (water, animal); green for human samples associated to HIV in adults; pink for children samples. Symbols refer to different Italian regions: Ab, Abruzzo; Ap, Apulia; Ca, Campania; ER, Emilia Romagna; FVG, Friuli Venezia Giulia; La, Latium; Lo, Lombardia; Ma, Marche; Pi, Piedmont; Sa, Sardinia; Si, Sicily; Tu, Tuscany; Ve, Veneto. Putignani and Menchella, 2010.

a model for *quantitative microbial risk assessment* (QMRA), the study confirmed that bathing in surface waters was actually associated with a significant risk of infection by *Cryptosporidium* or *Giardia*. This was especially the case for rivers not protected from human or animal fecal contamination. Surface waters, especially in rural areas, may be soiled by contaminated farmyard manure or slurry used as fertiliser for crop cultivation. Pasturing of infected livestock near crops or defaecation of infected undomesticated hosts onto them is an important factor for zoonotic contamination [7]. Also sludges, night soil, and raw waters may contribute to worldwide water pollution [97]. Recently, as inferred by outbreak surveillance data, recreational, drinking and fountain waters have been identified as important source of community infections worldwide (Table 4) [6]. In Ireland, as several recent waterborne outbreaks have shown (Table 4) [80, 98, 99] and as thoroughly discussed by the latest paper of Cheng et al., 2009 on the presence of *Cryptosporidium* and *Giardia* in wastewater treatment plants [100], cryptosporidiosis poses a significant threat to public health. In a recent study [51], performed on human stool samples collected in diversified geographical areas of Ireland, *Cryptosporidium* spp. were genetically characterised (Table 2). Overall, *C. parvum* was identified in 80% and *C. hominis* in 20% of cases, with an higher proportion in older age groups. *C. parvum* was the most common species in the rural, more sparsely populated West of Ireland and exhibited a pronounced Spring peak coincident with the peak of the national cryptosporidiosis incidence rate. The most common *C. parvum* subgenotype (Table 2) was the same detected in Irish cattle [101] confirming the prevalence of zoonotic *Cryptosporidium* transmission in Ireland.

In Holland, water in canals and recreational lakes are contaminated through the discharge of raw sewage from houseboats, sewage effluent, dog and bird feces. During two successive one-year study periods, the water quality in canals and recreational lakes was tested in Amsterdam with regard to the presence of fecal indicators and waterborne pathogens [102]. *Cryptosporidium* oocysts and *Giardia* cysts were detected both in canals and recreational lakes, despite conformity with the European bathing water legislation, indicating these parasites as health risk pathogens for situations of exposure to surface waters [102].

A significant study was undertaken to monitor the presence of *Cryptosporidium* and *Giardia* in water samples, including raw and treated waters from both surface and

Table 3: Public data sources exploited in the current study.

Site name	Link	Reference
International surveillance networks		
Neglected Diseases Initiative of the World Health Organization	http://www.who.int/neglected_diseases/en/	[59]
Center for Disease Control and Prevention	http://emergency.cdc.gov/agent/agentlist-category.asp	[93]
San Francisco Bay Area Cryptosporidiosis Surveillance Project	http://www.sfphes.org/water/index_crypto.htm	[136]
C-EnterNet (Canadian Integrated Enteric Disease Surveillance System)	http://www.phac-aspc.gc.ca/c-enternet/index-eng.php	[153]
Public Health Agency of Canada	http://www.phac-aspc.gc.ca/index-eng.php	[154]
FoodNet	http://www.cdc.gov/FoodNet/	[183]
Suites of free and open-epidemiology data source		
Tri-County Health Department	http://www.tchd.org/	[150]
AIDS site	http://data.unaids.org/en/default/asp	[161]
Communicable Diseases Branch	http://www.health.qld.gov.au/ph/cdb/default.asp	[245]
NetEpi	http://code.google.com/p/netepi	[273]
Epi Info software	http://www.who.int/chp/steps/resources/EpiInfo/en/index.html	[274]
Open-access peer-reviewed journals		
Euroserveillance Europe's Journal on infectious diasese epidemiology, prevention and control	http://www.eurosurveillance.org/	[63, 81, 98, 99, 178, 246–248, 276, 291, 292]
Center for Disease Control and Prevention: Morbidity and Mortality Weekly Report (MMWR)	http://www.cdc.gov/mmwr/	[92, 131, 132, 146, 156, 185–191, 249, 258, 260, 285, 293–295]
Public Health Agency of Canada	http://www.phac-aspc.gc.ca/surveillance-eng.php	[86, 296, 297]

ground sources in Portugal [103]. *C. parvum* was the most common detected species, followed by *C. hominis*, *C. andersoni*, and *C. muris*. These results are clearly suggestive of a wide distribution of *Cryptosporidium* spp. in source and treated waters in Portugal, with high occurrence of human-pathogenic *Cryptosporidium* genotypes (Table 2) [103, 104].

An important survey of sewage influent samples from 40 Sewage Treatment Works (STWs) throughout Norway were examined for *Cryptosporidium* oocysts and *G. duodenalis* cysts [105]. The data propose giardiasis as more widespread, and occurring with greater infection intensity than cryptosporidiosis: for *Cryptosporidium*, the highest estimate was up to 5 per 100 000 individuals in Eastern Norway while for *Giardia* 40 per 100 000 persons in Western Norway. Removal efficiencies at two STW with secondary treatment processes were estimated to be approximately 50% for *Cryptosporidium* and >80% for *Giardia*. A STW with minimal treatment had negligible removal of both parasites. Because many STW in Norway have indeed minimal treatment and discharge effluent into rivers and lakes [105], thus, risk of contamination of water courses by *Cryptosporidium* and *Giardia* represents a considerable risk in this country. Contamination from sewage discharges and wild or domestic animals are also important sources for untreated waters [97]. Both *Cryptosporidium* and *Giardia* are frequently found in the stool of domestic ruminants, especially young animals. Wild ruminants may serve as reservoirs for these zoonotic parasites, as inferred from an important cross-sectional survey conducted in Belgium to estimate the occurrence of *Cryptosporidium* and *Giardia* in captive wild young ruminants. The *Cryptosporidium* prevalence was 7.5% in the zoo animals and 3.7% in the bison from a commercial breeding farm [106].

In the Russian Federation, *Cryptosporidium* has been recently included in the *Index of the Epidemic Safety of Drinking Water* as new emerging pathogen, suggesting a growing attention to the parasite control also in geographical areas with no previous surveillance programs and dedicated studies [107].

3.2.1. Waterborne Cryptosporidodis in Italy. In Italy, an intense debate on the epidemiological and public health aspects of *Cryptosporidium* and *Giardia* infections has involved many researchers and has lead to investigate infection prevalence data especially on environmental and animal samples but less on human samples because cryptosporidiosis is not a notifiable disease in Italy [108–110] (Figure 5). Protocols recommended by the *National Institute of Health* are mainly used for detection of these protozoa

Table 4: Worldwide distribution of principal *waterborne*, **foodborne**, ***travel-related,*** and community outbreaks reported in the last decade (1998–2008): case characteristics.

Outbreak[1] type	Country	Ill[2]	Age	Likely causes for outbreak occurring	Species /genotype	Reference
			2008			
Foodborne	Finland	72 personnel of the Public Works Department in Helsinki	Adults	Salad mixture suspected	*C. parvum*	[178]
Foodborne	Sweden	21 guests and staff at a wedding reception	Adults	Sauce containing chopped fresh parsley	*C. parvum*	[179]
			2007			
Waterborne	Norway	89 hotel guests	Adults	In-house water contamination	*C. parvum*	[298]
Community	Scotland (UK)	6 veterinary students	Young adults	Lapse in hygiene, especially handwashing	*C. parvum* (subgenotype IIaA19G2R1)	[299]
Waterborne	England (UK)	57 swimming pool visitors	Children and adults	Swimming pool contamination	*C. parvum* *C. hominis*	[246]
Waterborne/ **foodborne**	Germany	201 soldiers	Young adults	Tap water/food contamination in a military field exercise	*C. parvum* (genotype 2)	[300]
Waterborne	Ireland (UK)	182	Adults	Contamination of treated water	*C. hominis* *C. parvum*	[98]
Waterborne	Sweden	800–1000	Children and adults	Contamination of an outdoor swimming-pool	*C. parvum*	[250]
Waterborne	ID (USA)	50 park visitors	Children and adults	Exposure to water from a splash feature	*C. hominis* (subgenotype IaA28R4)	[258]
			2006			
Waterborne	England (UK)	35 school people	Children and adults	Surface water contamination during a farm visit	*C. parvum*	[251]
Waterborne	CO (USA)	21 attendes to a pool party	Children and adults	Swimming, pool contamination	*C. hominis* (subgenotype IbA10G2)	[85]
Travelers' infection	FL (USA)	29 retired people	Elderly	Environmental contamination with animal feces	*C. parvum* (subgenotype IIaA16G1R1b)	[207]
Foodborne	ME (USA)	14 people	Not reported	Unknown	*Cryptosporidium* spp.	http://www.cdc.gov/foodborneoutbreaks/outbreak_data.htm
Foodborne	PA (USA)	2 people	Not reported	Unknown	*Cryptosporidium* spp.	
Waterborne	FL (USA)	9 children[3]	4 years[4]	Water fountain contamination	*Cryptosporidium* spp.	[261]
Foodborne	Japan	4 company members	Adults	Contamination of raw meat dish	*C. parvum* (genotype IIa)	[301]
			2005			
Foodborne	Denmark	99 company employees	Adults	Buffet salad eating	*C. hominis*	[180]
Community	Scotland (UK)	62 people	Adults and children	Outbreak linked to a wildlife centre visit	*C. parvum*	[247]
Waterborne	Wales (UK)	100	Mostly young adults	Contamination of raw and treated water	*C. hominis*	[291]
Waterborne	Turkey	191 inhabitants[5]	Children and adults	Contamination of water tank	*C. parvum*	[276]

Table 4: Continued.

Outbreak[1] type	Country	Ill[2]	Age	Likely causes for outbreak occurring	Species /genotype	Reference
			2005–2004			
Community	Spain	24 day-care children	Children	Children diaper use	*C. hominis*	[252]
			2004			
Waterborne	Norway	115[6]	Adults	Water supply contamination	*C. parvum* (bovin genotype, genotype 2, cervine genotype)	[277]
Community	Croatia	One family members	Elderly and adults	Nosocomial and person-to-person contamination	*C. hominis*	[302]
Waterborne	CA (USA)	273 park attendants	Children and adults	Contamination of a water park	*C. parvum* (genotype IIc)	[127]
Foodborne	NY (USA)	212 people[7]	Not reported	Contamination of unpasteurized apple cider	*Cryptosporidium* spp.	http://www.cdc.gov/foodborneoutbreaks/outbreak_data.htm
			2003			
Waterborne	Yorkshire and The Humber (UK)	66 people attending at the pool	Children and adults	Contamination of water at a public pool	*Cryptosporidium* spp.	[293]
Waterborne	South West (UK)	21 children attending at the water park	Children	Leisure facility of a 'water splash zone	*Cryptosporidium* spp.	[249]
Waterborne	South East of England (UK)	17 people attending at the pool	Children and adults	Contamination of water at a public pool	*Cryptosporidium* spp.	[249]
Waterborne	Midlands (UK)	122 people attending at the park	Children and adults	Contamination of a fountain water in a public park	*Cryptosporidium* spp.	[249]
Waterborne	South West of England (UK)	63 people attending at the animal centre	Children	Interactive water feature at an animal attraction centre	*C. parvum* (genotype 2)	[248]
Community	Wales (UK)	17 people attending at the school visit	Children and adults	Open farm, school visit	*C. parvum* (subgenotype IIaA15G2R1)	[79]
Community	Wales (UK)	36 people attending at the visit	Children and adults	Residential farmcentre, school visit	*C. parvum* *C. hominis* *C. meleagridis*	[63]
Waterborne	Majorca (Spain)	179 travellers	Children and adults	Hotel pool water contamination	*Cryptosporidium* spp.	[292]
Foodborne	OH (USA)	144 inhabitants	Children and adults	Contamination of unpasteurized apple cider	*C. parvum* subgenotype IIaA15G2R1, IIaA17G2R1	[182]
Community	MN (USA)	31 middle-/high-school students	Young people	Contact with calves	*C. parvum*	[303]
Community	MN (USA)	37 middle-/high-school students	Young people	Manure on hands	*C. parvum*	[303]
Foodborne	MN (USA)	9 people	Not reported	Contamination of food in a hotel banquet room	*Cryptosporidium* spp.	http://www.cdc.gov/foodborneoutbreaks/outbreak_data.htm

Table 4: Continued.

Outbreak[1] type	Country	Ill[2]	Age	Likely causes for outbreak occurring	Species /genotype	Reference
			2002			
Community	Yorkshire and The Humber (UK)	47 people attending at the nursery	Children and adults	Contamination at a day care nursery	*C. parvum* *C. hominis* *C. meleagridis*	[63]
Multiple exposure: *Waterborne* and Community	Wales (UK)	4 people	3 children and 1 adult	Contamination of a private drinking water supply private water supply, farm visits and personal contact	*C. parvum* (subgenotype IIaA17G1R1)	[79]
Waterborne	South East of England (UK)	21 people	Not reported	Contamination of a public drinking water supply	*Cryptosporidium* spp.	[293]
Waterborne	South East of England (UK)	31 people	Not reported	Contamination of a public drinking water supply	*Cryptosporidium* spp.	[293]
Waterborne	North West of England (UK)	50 school people[8]	Adults and children	Contamination of a private drinking water supply at a college	*Cryptosporidium* spp.	[293, 294]
Waterborne	Northern Ireland (UK)	29 people	Adults	Contamination of raw and treated water, and land surrounding the lake watershed	*Cryptosporidium* spp.	[99]
Community	Netherlands	Not reported	Children	Not reported, during a pet farm visit	*C. parvum* (genotype C1)	http://www.crypto-sporidium.it/
Community	NY (USA)	13 veterinary students	Young people	Hands contamination by calves contacts	*Cryptosporidium* spp.	[304]
Foodborne	FL (USA)	37 people	Not reported	Contamination of food in a hotel banquet room	*Cryptosporidium* spp.	http://www.cdc.gov/foodborneoutbreaks/outbreak_data.htm
Foodborne	GA (USA)	6 people	Not reported	Contamination of food in a private home	*Cryptosporidium* spp.	
			2001			
Waterborne	France	291 county inhabitants	Adults and children	Public water supply contamination	*C. hominis* (genotype Ib,Id) *C. parvum* (genotype IIa)	[84]
Waterborne	France	573	Adults	Contamination of tap water	*C. parvum* (genotype 1)	[305]
Waterborne	South West of England (UK)	14	Adults and children	Contact with astream at a beach	*Cryptosporidium* spp.	[294]
Community	South East of England (UK)	30	Adults and children	Contamination at a day care nursery	*Cryptosporidium* spp.	Unpublished data
Waterborne	South East of England (UK)	152 people attending at a school[8]	Adults and children	Contamination of outdoor school pool water	*Cryptosporidium* spp.	[294, 295]
Waterborne	Canada (USA)	1039 people	Young adults	Contamination of drinking water	*C. parvum*	[296]
Waterborne	Canada (USA)	59 people attending an Ukrainian dance festival	Adults	Contamination of a swimming pool in a hotel	*C. parvum*	[297]
Waterborne	(IL) USA	358 waterpark attendants	Adults and children	Contamination of waterpark and person-to-person contact	*C. hominis* (genotype Ia)	[259]

Table 4: Continued.

Outbreak[1] type	Country	Ill[2]	Age	Likely causes for outbreak occurring	Species /genotype	Reference
Foodborne	Queensland (Australia)	8 inhabitants	Children	Contamination of drinking unpasteurised milk	*Cryptosporidium* spp.	[262]
Community	New Zealand	20 farm inhabitants	Children	Hand contamination by calve contact	*Cryptosporidium* spp.	[264]
Community	Tasmania (Australia)	36 participants at the agricultural show	Adults	Contamination associated with an animal nursery	*Cryptosporidium* spp.	[306]
Community	Brazil	224 day care attendants	Children	Person-to-person contact	*C. hominis* (genotype 1)	[307]
			2001–2000			
Waterborne	Northern Ireland (UK)	347	Adults	Contamination of drinking water	*C. parvum* (bovine genotype; human genotype)	[80]
Waterborne	Haiti	93 patients	Adults and children	Contaminated water and overcrowded conditions of urban slums	*C. hominis*, *C. parvum*, *C. felis*	[69]
			2000			
Waterborne	England and Wales (UK)	58	Adults	Contamination of drinking water	*C. parvum* (genotype 2)	[308]
Waterborne	England and Wales (UK)	207	Not reported	Contamination of drinking water	*C. hominis* and *C. parvum* alleles	[309]
Waterborne	Yorkshire and The Humber (UK)	41 people attending a public pool	Adults and children	Contamination of pool water	*C. parvum* (subgenotype IIaA17G1R1)	[79, 295]
Waterborne	Majorca (Spain)	>250	Adults and children	Contamination of a hotel pool water	*Cryptosporidium* spp.	[81]
Community	Netherlands	Not reported	Children	School children visiting a pet farm	*Cryptosporidium* spp.	http://www.crypto-sporidium.it/
Foodborne	IL (USA)	8	Not reported	Contamination of coleslaw in a private home	*C. parvum*	http://www.cdc.gov/foodborneoutbreaks/outbreak_data.htm
			1999			
Waterborne	Russia	50	Adults	Contamination of drinking water	*Cryptosporidium* spp.	[310]
Waterborne	FL (USA)	38 park visitors	Adults and children	Contamination of a water fountain	*Cryptosporidium* spp.	[260]
			1998			
Waterborne	Spain	21	Children	Contamination of tap water	*Cryptosporidium* spp.	[253]
Foodborne	DC (USA)	88 students and employees	Young adults and adults	Contamination of food by a food handler in a cafeteria	*Cryptosporidium* spp.	[311]

[1] In presence of two or more cases of similar infection, with a common exposure in the community not related to waterborne or foodborne diasese, the term of community disease was used.
[2] Number and category of people with symptom referable to cryptosporidiosis.
[3] This outbreak was characterised by a *Cryptosporidium* infection in 9 of the 11 children, a coinfection of *Giardia* and *Cryptosporidium* in 2 of the 11 children and a concomitant infection of other 38 additional children by only *Giardia* oocysts triggered by the same likely source.
[4] Median age.
[5] Outbreak characterised by a concomitant waterborne *Cyclospora* outbreak.
[6] Outbreak characterised by a concomitant waterborne *Giardia* outbreak.
[7] Outbreak characterised by a concomitant foodborne *E. coli* O111 outbreak.
[8] Outbreak characterised by a concomitant waterborne Norovirus outbreak.

in raw and drinking water while other no well-standardised procedures are available for wastewater [109]. However, raw, reclaimed and drinking water are not subjected to routine monitoring. In surface waters (rivers, watersheds, watercourses and lakes), several studies have reported high contaminations by (oo)cysts of *Giardia* and *Cryptosporidium* all over the peninsula with the highest prevalence for *Giardia* [111–114]. Presence of both *Cryptosporidium* and *Giardia* has been monitored in sewage, surface waters, drinking water, and swimming pools by simultaneous tracing of bacterial indicators. In the Latium and Apulia regions, cysts and oocysts were detected in sewage and surface water, with *Giardia* numbers always prevailing over *Cryptosporidium*, but not in drinking waters. However, remarkably, *Cryptosporidium* was detected in 9% of samples collected from swimming pools in the Latium [112]. The paper by Di Benedetto et al., 2005 [113] described the occurrence of *Cryptosporidium* and *Giardia* (oo)cysts in water samples of two municipal treatment plants, and in surface and ground water wells in Sicily. The wastewater samples taken before and after treatment process were assayed over the course of one year: *Giardia* cysts were detected in all samples throught the year at higher concentration levels than *Cryptosporidium* oocysts, subjected to a peak during Spring. Cysts were detected in one lake at very low concentration; on the contrary, both parasites were found at high-concentration levels in all samples collected through one year from the river waters. The pattern of occurrence of both parasites showed temporal-related relationship to rainfall trend (Table 1) (Figure 3). In the Tuscan area, five drinking water treatment plants, differing for the employed handling, were monitored for the presence of *Cryptosporidium* and *Giardia* (oo)cysts, to estimate the removal capacity of each plant [114]. Water samples (from inflow raw water and outflow drinking water) were analysed during a one-year survey and both protozoa were detected. The occurrence of (oo)cysts was not associated with seasonality, turbidity or *C. perfringens*, but however low performance of plants was correlated with presence of protozoa in outflow drinking waters. *Giardia* cyst and *Cryptosporidium* oocyst removal efficiency was also evaluated in a wastewater tertiary treatment system based on membrane ultrafiltration and fed with secondary-treated municipal wastewater in Apulia: *G. duodenalis* and *C. parvum* were identified in feed water but were found in filtered water only during occasional failure of the filtration system [115]. Also in raw sewage and primary effluent more *Giardia* cysts than *Cryptosporidium* oocysts were detected in many monitoring studies [112, 113, 116, 117].

Annual rainfall reduction in some regions and increased human consumption have caused a shortage of water resources at global level. The recycling of treated wastewaters has been therefore suggested for domestic, industrial, and agricultural activities. *Giardia* and *Cryptosporidium* are known to be highly resistant to water treatment procedures and to cause outbreaks through contaminated raw or treated water. The study by Cacciò et al., 2003 [117] performed an investigation in four wastewater treatment plants in Lombardia, Campania, Sardinia, Sicily by sampling wastewater at each stage of the treatment process over the course of one year, and testing the presence of both parasites. While *Cryptosporidium* oocysts were rarely observed, *Giardia* cysts were detected in all samples throughout the year, with peaks observed in Autumn and Winter. The massive amounts of feces from humans and animals are discharged, dumped, or carried in runoff, bringing encysted zoonotic protozoan parasites to estuaries and coastal waters, where they contaminate bathing beaches, and are finally filtered and concentrated by shellfish eaten by humans and marine mammals, and infect a wide range of marine animal hosts, resulting in morbidity and mortality to some populations [118]. Therefore, nearshore marine sites may be considered at higher risk for exposure to livestock runoff, human sewage, or both fecal sources. Bivalves filter large volumes of water and can concentrate organisms which are pathogenic for humans and animals. In a recent paper [119] the presence of *Cryptosporidium* spp. in clams (*Chamelea gallina*) from the Adriatic coast (Abruzzo) was reported for the first time. The temporal occurrence of *Cryptosporidium* (*C. hominis* and *C. parvum*) oocysts in *Ruditapes philippinarum* were evaluated in two farms located in Veneto and in Friuli Venezia Giulia [120]. The paper of Giangaspero et al., 2009 [121], has simultaneously investigated the presence of *Giardia* and *Cryptosporidium* in inflowing water and harvested shellfish (*Ruditapes decussatus* and *Mytilus galloprovincialis*) in geographically closed environment (Varano Lagoon, Apulia). Higher concentrations of *Giardia* cysts than *Cryptosporidium* oocysts were registered in almost all wastewater and water samples, but testing of shellfish gave negative results for both protozoa. However, *Cryptosporidium* (*C. parvum*, *C. felis*, *C. andersoni*, and two novel genotypes) was detected in haemolymph samples from mussels in California [122]. In this paper, factors significantly associated with detection of *Cryptosporidium* spp. in mussel batches were exposure to freshwater outflow and collection within a week following a precipitation event, while no correlation was found with exposure to livestock feces or human sewage sources. Remarkably, mussels were proposed as tracer to monitor water quality, suggesting that humans and animals ingesting shellfish may be exposed to both host-specific and anthropozoonotic *Cryptosporidium* genotypes of public health significance [122].

In the last decade, a major concern for the scientific community has been whether infected animals can serve as reservoirs of *Giardia* and *Cryptosporidium* infection for humans. The paper by Giangaspero et al., 2007 [109], presented data on prevalence and molecular genotyping from several sample types (companion animals, sheep, cattle, goats, wastewaters, surface water, shellfish, and humans) collected in the Italian territory. Several species/genotypes of *Cryptosporidium* have a relevant zoonotic potential and ruminants may be important sources of infection for human beings [106, 108]. Cryptosporidiosis causes important economic losses to animal husbandry and livestock production. To obtain information on the occurrence of cryptosporidiosis in lambs and the potential zoonotic role of the *Cryptosporidium* isolates, fecal samples collected from lambs in Central Italy (Abruzzo) were examined for the presence of *Cryptosporidium* and discussed in the paper

by Paoletti et al., 2009 [123]. All positive samples were characterised as zoonotic *C. parvum* genotype suggesting a potential public health hazard in Italy. Also the risk related to bovine zoonotic contribution was studied by Duranti et al., 2009 [124] by considering 248 farms in Central Italy (Latium and Marche). In all positive samples, the etiological agent was identified as *C. parvum* with a large subtype genetic variability. The prevalence of farm infection ranged from 3.4% to 35.6% and appeared related to putative risk factors such as farm type, calve stalling, late supply of colostrum, number of heads and contact between calves and adults. However, the highest risk was associated with housing calves separately from their dams, whereas dam nursing resulted as a protective factor. This important evidence consistently agrees with the role of maternal milk as protective factor against cryptosporidiosis onset both in animals [125] and in humans [126].

3.3. Waterborne Cryptosporidosis in USA and Canada. Besides zoonotic transmission, an important identified waterborne infection route is linked to recreational waters [6]. A cryptosporidiosis outbreak from August to September 2004 in California, affected more than 250 people visiting a waterpark [127] (Table 4). Occurring more than a decade after the first reported outbreak of cryptosporidiosis in a swimming pool [128], this outbreak demonstrates that recreational waters may represent a highly potential infection vehicle especially in childhood. Recently in USA *Cryptosporidium* species have emerged as a major cause of outbreaks of diarrhoea [6] and have been associated with consumption of contaminated recreational and drinking waters and with the attendance to child-care programmes [129]. Principal risk factors for infection seem to coincide with swallowing untreated water from a lake, river, or after exposure to recreational water or, remarkably, after contact with a child in a child-care programme or with diapers [129] (see Section 7). Although exposure to recreational water is commonly implicated in summertime cryptosporidiosis outbreaks, this evidence demonstrates that investigations of increased incidence of cases in Summer should also examine other potential risk factors, addressing the multiple transmission routes for *Cryptosporidium*. The extended review of Craun et al. 2005 [130], on outbreaks associated with recreational water during 1971–2000 in USA, provided evidence that bacterial or protozoan etiology was identified in three-quarters of the outbreaks. Outbreaks caused by *Cryptosporidium* and *Giardia* were primarily associated with treated water in swimming and wading pools. Contamination from sewage discharges and wild or domestic animals were also recognized as important sources for untreated waters. Contributing factors in swimming-pool outbreaks were inadequate attention to maintenance, operation, disinfection, and filtration [131]. For the 764 waterborne outbreaks registered from 1971 to 2002 by the USA *National Surveillance of outbreaks* and associated with drinking water, 575 457 cases of illness and 79 deaths were reported [132, 133]. If properly applied, current protocols in municipal water treatment are effective at eliminating pathogens from water. However, inadequate, interrupted, or intermittent treatment has repeatedly been associated with incidence of waterborne disease outbreaks. Contamination is affected by the number of pathogens in the source water, the age of the distribution system, the quality of the delivered water, and climatic events that can tax treatment plant operations. Furthermore, private water supplies are not regulated by the USEPA and are generally not treated or monitored [134].

A case-control study [135] was conducted in the San Francisco Bay Area as part of a national study sponsored by the CDC [136] (Table 3) to ascertain the major routes of transmission for endemic cryptosporidiosis, with an emphasis on evaluating risk from drinking water. Drinking and recreational water, food items, travel, animal contact, person-to-person fecal contact, and (for adults) sexual practices were evaluated as major exposures. The study showed no significant association between cryptosporidiosis and drinking water among the immunocompetent population in the San Francisco Bay, and therefore, the key risk factor for cryptosporidiosis in this area was identified in travelling to another country [135].

The recent paper by Reynolds et al., 2008 [137] has provided estimates of waterborne infection and illness risks in the USA by considering the correlation between the total number of water systems, source water type, total populations exposed, and microbial infection. The results indicated 10.7×10^6 and 2.2×10^6 infections/year in populations served by community and noncommunity groundwater systems, respectively, and 26.0×10^6 infections/year in populations with municipal surface water system services. Water purification technologies applied at the *point-of-use* (POU) could be effective for limiting the effects of source water contamination, treatment plant inadequacies, minor intrusions in the distribution system, or deliberate posttreatment acts as bioterrorism (i.e. *Cryptosporidium* is a Category B bioterrorist threat) [93]. However, epidemiological studies are conflicting on the benefits of POU water treatment compared to untreated tap water [138–141]. Nevertheless, for immunocompromised and other populations, including those experiencing physiological life stages such as pregnancy, or those very young or very old, POU devices may represent water treatment options for reducing risks of *Cryptosporidium* and other types of infectious agents transmitted by drinking water. A study [142], aimed to estimate the urban contribution to the total *Cryptosporidium* and *Giardia* receiving-water loads in USA, was focused on *combined sewer overflows* (CSO), discharges of mixed untreated sewage and stormwaters. Interestingly, CSO from urban areas was not found to be a significant contributor of *Cryptosporidium*, but a significative source of *Giardia* [142]. Most cryptosporidiosis outbreaks in the USA are caused by *C. hominis*, and this species is often reported as the primary cause of cryptosporidiosis in this country [143, 144]. However, outbreaks account for only 10% of the overall cryptosporidiosis cases, and there are still few data on the species causing sporadic cases [145] (Table 2). The highest incidence of cryptosporidiosis in the USA has been found in the upper Midwest States [146]. In particular, Wisconsin was reported as having the highest

incidence of cryptosporidiosis every year from 1999 to 2002 [146]. The Wisconsin city of Milwaukee also had the largest cryptosporidiosis outbreak in 1993, where more than 400 000 people were infected following contamination of the municipal water supply [147]. The pivotal study by Feltus et al., 2006 [148], identified for 49 cases of sporadic cryptosporidiosis in Wisconsin, during the period from 2003 to 2005, *C. parvum*, *C. hominis*, a cervine genotype [64], a cervine genotype variant, and a new W17 human genotypes [149] (Table 2). However, the study showed that most cases were linked to zoonotic *Cryptosporidium* genotypes. The Tri-County Health Department of Colorado [150] (Table 3) investigated an outbreak of cryptosporidiosis occurred in 2006, linked to a community swimming pool treated by chlorination and UV light irradiation. Risk factors appeared through swimming, getting water in mouth, and swallowing water. Important studies on waterborne-transmitted infections have been also conducted in Canada. In South Western Ontario, from July 2002 to December 2003, water samples were collected from 36 locations within the Grand River Watershed, and were analyzed for total coliforms, fecal coliforms, *E. coli*, *E. coli* O157:H7, thermophilic *Campylobacter* spp., culturable human enteric viruses, *C. perfringens*, *Cryptosporidium* spp., and *Giardia* spp. [151]. Peaks in pathogen numbers frequently preceded the peaks in numbers and turbidity of indicator organisms suggesting important implications (e.g., pathogen transport model) for designing monitoring programs in source water risk assessment [151]. In Southern Ontario, to identify management practices associated with an increased within-herd prevalence of *C. parvum* shedding on dairy farms, a large study was conducted on fecal samples collected from 1089 calves in 119 herds [125]. Overall, 30% of the calves were shedding *C. parvum* oocysts, with a prevalence ranged from 0 to 80% within herds and at least one positive calf detected in 77% of herds. Predictors significantly associated with an increased prevalence of shedding were the use of calf rub prophylaxis in cows and the feeding by milk replacer in the first week of life. In contrast, the presence of concrete flooring in calf housing areas and the use of soap or detergent when washing calf feeding utensils appeared to be protective [125].

The QMRA model was recently applied to assess the relative risks of infection associated with the presence of *Cryptosporidium* and *Giardia* in drinking water in Canada [152]. The assessment of the final risk in the contamination of the water plants resulted considerably affected by the selection of treatment performance model (filtration and ozonation). Recently, data from a sentinel site (Waterloo Region, Ontario) of the C-EnterNet (Table 3) [153, 154] were used to assess exposure factors on laboratory-confirmed *Cryptosporidium* infections [155]. Of 1204 cases of enteric illness in the sentinel area between April 2005 and December 2007, 36 cases were selected after excluding outbreak and international travel-related cases. Cryptosporidiosis was associated with swimming in a lake or river, drinking municipal water, and having a family member with a diarrhoeal illness. Since 1971, the *Waterborne Disease and Outbreak Surveillance System* has reported on *waterborne disease and outbreak* (WBDO)-related data. In 1978, WBDOs associated with recreational waters (natural and treated waters) were added [156]. During 2003-2004, a total of 62 WBDOs associated with recreational water were reported by 27 states, with typical illness occurred in 2,698 persons, resulting in 58 hospitalizations and one death [156]. Of the 62 WBDOs, 30 were outbreaks of gastroenteritis and *Cryptosporidium* was confirmed as the causal agent in 11, and all except one of these outbreaks occurred in treated water venues [156] (Table 4). Lastly, approximately 90% of waterborne outbreaks occur in treated recreational waters (swimming pools, spas and recreational parks), while the remaining 10% arise from natural waters used for leisure (e.g., bathing in rivers, beaches, etc) [6].

3.4. Waterborne Cryptosporidiosis in New Zealand and Australia. New Zealand has a higher incidence of cryptosporidiosis compared to other developed countries. A recent study in [157] aimed to thoroughly describe the epidemiology of this disease and to identify specific potential risk factors by analysing anonymous cryptosporidiosis notification and hospitalisation data. Human cases were designated as "*urban*" or "*rural*" and an association between disease rates and animal density was studied. Over the 10-year period from 1997 to 2006, the average annual rate of notified cryptosporidiosis was 22 cases per 100 000 population. The number of hospitalisations amounted to 3.6% of the notified cases. The annual incidence of infection appeared fairly stable, but showed marked seasonality with a peak rate in Spring. The highest rates were among Europeans, children 0–9 years of age, and those living in low-deprivation areas (Table 1) (Figure 3). Notification rates showed large geographic variations, with rates in rural areas 2.8 times higher than in urban areas, and with rural areas also experiencing the most pronounced Spring peak, correlated with farm animal density. Therefore, most transmission of *Cryptosporidium* in New Zealand appears to be zoonotic in rural settings [157]. These data seem to corroborate the evidence that the proportion of *C. parvum* sporadic cases in humans is higher in rural than in urban areas [158] and confirm the variation of the geographical distribution of *Cryptosporidium* infections within countries [159]. In New South Wales (NSW, Australia) the subtypes have global distributions and indicate both anthroponotic and zoonotic transmission routes in sporadic cryptosporidiosis [160].

3.5. Waterborne Cryptosporidiosis in African Developing Countries. The burden of disease from cryptosporidiosis in developing countries is in the Sub-Saharan Africa, because of the disseminated status of malnutrition in children and the highest world prevalence of HIV infection in this region, with peaks reaching the 15%–28% of the adult population [161] (Table 2). However, in this vast geographical area, *Cryptosporidium* and *Giardia* infections are rampant also in adult and immunocompetent populations, due to the unhygienic and improper disposal of wastewater and to the use of surface waters as major source of potable water. The important research by Gideon et al. 2007 [162], represents

a preliminary attempt to isolate, identify, and quantify recurrent forms of these emerging protozoa in the waste and surface waters in Cameroon. The cyst and oocyst counts were higher in the direct effluent because they were released directly into the wastewater by feces, while they were diluted in the surface water, reducing their abundance [162]. Clearly the nonfunctional water purification stations and ineffective water treatment systems expose the community to potential outbreaks; however, surveillance plans are still completely lacking. In North Africa cryptosporidiosis is prevailingly monitored as public health issue and, recently, a comprehensive review of *C. parvum* epidemiology has been produced with the aim to describe the burden associated with cryptosporidiosis among Egypt and close countries [163]. *C. parvum* prevalence ranged from 0%–47%. Remarkably, identified risk factors, including population, ecology, and environmental findings, suggested water and zoonotic transmission modalities as the principal route of infection [163]. A recent paper [164] has provided evidence on the link between diarrheal diseases of humans and young calves in the Middle East (Iran). By exploiting genotyping approach, the authors have inferred both anthroponotic and zoonotic transmission of cryptosporidiosis in this geographical area [164] (Table 2).

3.6. Waterborne Cryptosporidiosis in Asia. In Asia, the emerging need to facilitate the characterization of the endemic transmission of cryptosporidiosis has recently provided a large study [41] on genotype distributions of *Cryptosporidium* oocysts in domestic wastewater in China (Table 2). Raw domestic wastewater samples were collected from four wastewater treatment plants in Shanghai, from December 2006 to April 2007. Interestingly, diverse *Cryptosporidium* species/genotypes were identified and *C. hominis* subtyping revealed a high complexity of *Cryptosporidium* populations often unique (Table 2) (see Introduction, Section 1.6).

The specific contribution of the zoonotic transmission of *Cryptosporidium* in China was discussed in the recent paper by Liu et al., 2009 [165], in which a total of 507 fecal specimens from six dairy farms were examined for *Cryptosporidium* spp. Interestingly were identified *C. andersoni* and *Cryptosporidium ryanae* [166], a new species described from cattle and previously identified as the *Cryptosporidium* deer-like genotype [167], with *C. andersoni* as the dominant species. This interesting distribution of *Cryptosporidium* spp. may support the idea of unique species and transmission in these areas. In Taiwan, cryptosporidia were detected in most of the surface water specimens [168]. Water samples collected from potable water treatment plants were investigated for the presence of *Giardia* cysts and *Cryptosporidium* oocysts. The frequency of occurrence of (oo)cysts was 78% for *Giardia* and 72% for *Cryptosporidium* in 18 raw water samples. Ten out of 13 samples collected from treated water samples showed the presence of cysts, while oocysts were detected in five out of 13 treated water samples. The risk assessment for the presence of cysts and oocysts, indicates the possibility of waterborne transmission of *Giardia* and *Cryptosporidium* infection in Taiwan where adequate water treatment is almost absent. In India, an important work [169] reported on the correlation between infections in livestock and seasonal rainfall by considering the monsoon period impact on cryptosporidiosis. The survey revealed a 30% infection with *C. parvum*, out of 457 fecal samples collected from neonatal bovine calves (0–3 months of age) from dairy farms for one year, across three different geographical and agro-climatic areas of India (Northern subtemperate, Eastern subtropical, and Southern subtropical region), and through the premonsoon, monsoon and post-monsoon periods. The infection was more prevalent in the Northern parts of the country than in the Eastern or Southern areas, and *C. parvum* was detected as the only species [169]. Highest prevalence was recorded during monsoon months. A more recent study [170], however, performed on 350 fecal samples collected from juvenile and mature cattle (6–24 months of age), across the three representative agro-climatic regions of the country, showed the only presence of *C. andersoni* with the highest occurrence in the Northern states [170]. The animals between age group of 6–12 months were mostly affected and the seasonal prevalence was higher during the hot and humid monsoon season, followed by the premonsoon season when the climate is hot and humid. However, consistently with Paul et al., 2008 [169], in the post-monsoon season the prevalence dropped, providing evidence for transmission related to survivability of the infective stages of the parasite [46]. The results seemed to suggest that *C. andersoni* is the major *Cryptosporidium* species affecting cattle with the increase in age, despite differences in species may also be associated to geography differences in sampling. However, unlike previous studies [169, 171], no cases of *C. parvum*, *C. bovis* and *Cryptosporidium* deer-like genotype [167] were found in the report of Paul et al., 2009 [170], evidence which may be ascribed to specific prevalence pattern of *C. andersoni* in the areas and season undertaken for study, corroborating the idea of space and time frames for transmission [36]. The animal age undoubtedly remains the most effective risk index in investigating veterinary transmission of *Cryptosporidium* [46]. Livestock fecal pollution of water sources appears to be the leading cause for both outbreaks and sporadic cases of cryptosporidiosis in developing countries, as already reported in high-income countries [159, 172, 173].

3.7. Waterborne Cryptosporidiosis in South and Central America. To study the prevalence of *Cryptosporidium* infection, levels of anti-*Cryptosporidium* IgG antibodies were measured among people inhabiting neighbourhood of a periurban area in the Northeast of Brazil [174]. The study aimed to investigate the effects of environmental sanitation measures, hygienic habits, and household water supply, storage and handling on the frequency of these antibodies in the population sera, providing a model for low-income countries. *Cryptosporidium* interhousehold transmission was studied by comparing the frequency of anti-*Cryptosporidium* IgG antibodies among people inhabiting areas with or without different environmental sanitation measures and intrahousehold transmission by comparing the presence of these

antibodies in families with or without cases of diarrhoea, associated with the presence of *Cryptosporidium* oocysts in stools. A statistically significant difference was detected in the prevalence of *Cryptosporidium* infection between areas without and with environmental sanitation measures. Positive associations were found between poor household water supply, drinking unboiled/unfiltered water and high levels of anti-*Cryptosporidium* antibodies in sera, suggesting uncorrected household water supply, storage and handling as an important factor on *Cryptosporidium* transmission in developing countries cities [174].

In Central Mexico, the economy of the country is strongly based on sheep and bovine farm management and preventive veterinary medicine represents a useful approach to identify risk factors for zoonotic transmission. To establish the relationship between sheep farm management practices and cryptosporidiosis in this country, 37 farms were mapped to highlight facility characteristics, cleaning measures, water use and animal management practices [175]. Five indexes showed statistical significance: (i) watering frequency; (ii) bottle cleaning frequency; (iii) forage storage; (iv) place of parturition; (v) grazing place. The latter index provided the most relevant association between management practices and cryptosporidiosis. Grazing place may represent a crucial risk factor for cryptosporidiosis in Mexico, contributing to understanding how domestic animals and wildlife cycles interact, resulting in human infections and endemic locations.

3.8. Conclusions. Advanced molecular tools and improvement of international surveillance networks (Table 3) are now beginning to answer epidemiological questions related to waterborne transmission which is still difficult to address by traditional methods**.** Indeed environmental sampling surveys are often hampered by the absence of proper technologies able to provide reliable water sampling collections. Furthermore, many geographical gaps need to be filled to evaluate worldwide waterborne infection distributions and to assess the relationship between animal, human fecal wastes, and water transmission both in undeveloped and developed countries.

4. Cryptosporidiosis a "Foodborne Disease"

4.1. Food-Related Routes. In our analysis of *Cryptosporidium*-linked outbreaks, 15 out of 71 (21.1%) appear to be correlated to foodborne transmission, with a higher number of outbreak episodes in 2006 and 2008. Geographically, the outbreaks seem to be concentrated in the USA, Canada, and Australia and in North Europe, especially Finland and Sweden (Table 4) (Figure 4). Many infection routes have been identified, as consuming salad vegetables washed by contaminated water, eating raw meals, using contaminated water for making ice and frozen/chilled foods, or making products which receive minimum heat or preservative treatment (Table 4). However, contact with contaminated feces transmitted by coprophagoustransport hosts (e.g., birds and insects), worker aerosols (from sneezes), and exposed hand lesions have also been associated with outbreaks [176]. Transfer of pathogens has been documented through contaminated fabrics and carpets, rings, currency, skin surfaces, dust, and aerosols and though person-to-person transmission [176].

4.2. Foodborne Cryptosporidiosis in Europe. In the 27 member states of the European Union, zoonotic parasites transmitted by food are circulating with different prevalence according to the country, the environmental conditions, the human behaviour, and the socioeconomic level. Foodborne parasites can be divided into two main groups according to human transmission. They reach the human beings through the consumption of raw infected food such as muscle tissues of different animal species (*T. gondii*, *Sarcocystis hominis*, *Sarcocystis suishominis*, *Diphyllobotrium latum*, *Taenia solium*, *Taenia saginata*, *Opisthorchis felineus*, *Anisakis* spp., *Pseudoterranova* spp., *Trichinella* spp.), or vegetables (*Fasciola hepatica*), and contaminated food and water resources (*G. duodenalis*, *Cryptosporidium* spp., *T. gondii*, *Echinococcus granulosus* sensu latu, *Echinococcus multilocularis*, *T. solium*, *Taenia multiceps*) [177]. Remarkably, foodborne outbreaks of cryptosporidiosis are considerably increasing in Northern Europe, as shown by the two important outbreaks registered in Finland and Sweden during 2008 [178, 179] (Table 4) (Figure 4).

In 2005 an outbreak of diarrhoea, affecting a group of 99 company employees, was described near Copenhagen [180] (Table 4). All people were ill and 13 positive for *C. hominis* infection. Disease was associated with eating from the canteen salad bar on one, possibly two, specific weekdays. Three separate salad bar ingredients were found to be likely sources: peeled whole carrots served in a bowl of water, grated carrots, and red peppers. An anthroponotic route of infection was speculated, triggered by a person excreting the parasite which may have had contaminated the buffet [180].

In Norway a searching for parasites in fruits and vegetables was undertaken in the period from 1999 to 2001 [16]. Of the 475 samples, 29 were found to be positive for *Cryptosporidium* oocysts and *Giardia* cysts, while 19 only for *Cryptosporidium* (lettuce and mung bean sprout samples). Mung bean sprouts were significantly more likely to be contaminated with *Cryptosporidium* oocysts or *Giardia* cysts than the other fruits and vegetables, despite concentrations were generally low (approximately 3 (oo)cysts per 100 g product). There was no association between imported produce and detection of parasites. *Crvptosporidium* oocysts and *Giardia* cysts were also detected in water samples concerned with field irrigation and production of bean sprouts [16]. This was the first report on detection of parasites in vegetables and fruit obtained in a highly developed wealthy country, without there being an outbreak situation.

4.3. Foodborne Cryptosporidiosis in USA and Canada. Generally, viruses and encysted parasites are more resistant than enteric bacteria to adverse environmental conditions, but all pathogens can survive long enough for transfer from a contaminated worker to food and food contact surfaces

[176]. Also outbreaks associated with consumption of fruit juice have been growing as an emergent public health problem since the early 1990s, when the first outbreak associated with apple cider was described [181]. However, in the period from September to November 2003, 12 local residents in Northern Ohio were diagnosed with cryptosporidiosis for having drunk ozonated apple cider [182] (Table 4). In response to epidemiologic investigations of outbreaks in which juice is implicated, the USA Food and Drug Administration (FDA) has implemented process control measures to regulate the production of fruit juice, according with the *Hazard Analysis Critical Control Point* (HACCP) plan. However juice operations that are exempt from processing requirements or do not comply with the regulation continue to be implicated in outbreaks of illness. The CDC receives reports of food-associated outbreaks of illness (Table 3) [183] and its *Foodborne Outbreak Reporting System* has reviewed, from 1995 through 2005, ten implicating apple juice or cider, eight linked to orange juice, and three involving other types of fruit juice-associated outbreaks. Among the 13 outbreaks of known etiology, two were caused by *Cryptosporidium* and one by Shiga toxin-producing *E. coli* O111 and *Cryptosporidium* [184] (Table 4). The incidence of foodborne disease outbreaks caused by contaminated low-pH fruit juices is highly increasing [185]. The association of *Cryptosporidium* with fruit juice is raising a safety concern in food industries. In 1998, CDC implemented enhanced surveillance for foodborne-diseases outbreaks (FBDOs) by increasing communication with state, local, and territorial health departments and revising the outbreak report form. Since 2001, reports of FBDOs are submitted through a web internet application called *electronic Foodborne Outbreak Reporting System* (eFORS) (Table 3) [183, 185–191].

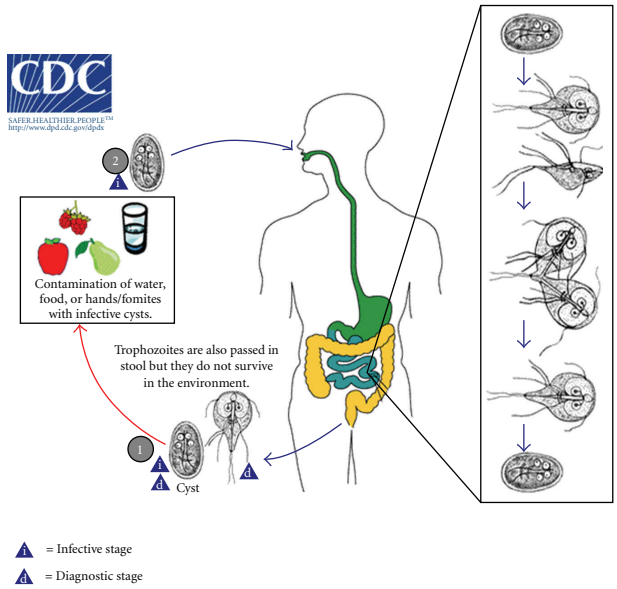
4.4. Foodborne Cryptosporidiosis in South and Central America. In Central America there is a high attention to foodborne infections. Recently, the role of the food handlers has been investigated in Venezuela, where cryptosporidiosis is an important public health problem [192]. Despite a basic investigation approach, fourteen out of 119 fecal samples from food workers were found positive for *Cryptosporidium* spp. and associated with other protozoa, being most frequent *Endolimax nana*, followed by *B. hominis*, *Entamoeba coli*, *G. lamblia,* and *E. histolytica*/*Entamoeba dispar*. In the paper of Calvo et al. 2004, [193] lettuce, parsley, cilantro, strawberries and blackberries circulating in local agricultural markets of the Central Valley of Costa Rica were investigated for the presence of *Cryptosporidium* spp., *Cyclospora* spp., and Microsporidia. Fifty different samples of each product, 25 taken in the dry season and 25 in the rainy season and coming from five different local agricultural markets, were evaluated. Although all vegetables presented fecal coliforms in high concentrations, lettuce and cilantro presented a statistical difference between the rainy and the dry season, being greater during the rainy season. Fecal coliforms were not detected in strawberries and blackberries probably due to its low pH. All products presented *Cryptosporidium* spp., *Cyclospora* spp., and Microsporidia. *Cryptosporidium* was not present in strawberries. Microsporidia were present in all products except blackberries and *Cyclospora* was only isolated from lettuce during the dry season. These results show the importance of introducing good agricultural practices, especially due to the resistance of *Cryptosporidium* and *Cyclospora* to disinfecting agents [193].

4.5. Conclusions. The considerable presence of *Cryptosporidium* in diversified food matrices makes it imperative to develop appropriate prevention strategies for food safety and suitable molecular techniques for parasite identification. As a general role, the control strategies should be based on the education of the consumers, farmers, and shepherds, the improvement of farming conditions, the improvement or the development of more sensitive methods to detect these parasites in slaughtered animals and in foodstuff, a control of sewage sludge on pastures and of drinking water resources, and the reduction of contacts between livestock and wild animals which frequently represent the most important reservoir of these pathogens [177].

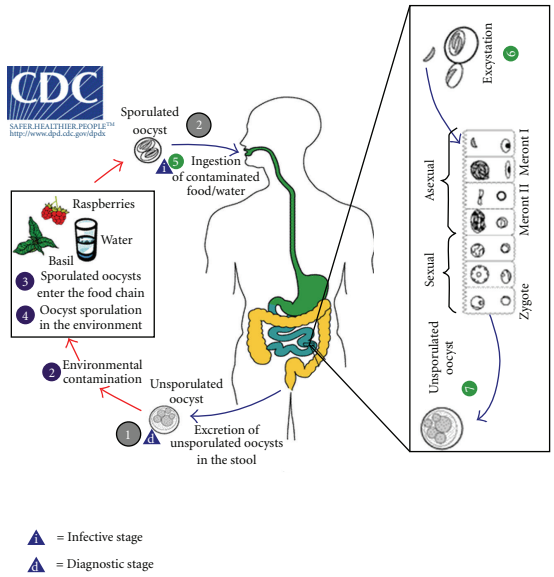
5. Cryptosporidiosis a "Travelers' Disease"

5.1. Traveler's Diarrhoea and Main Pathogen Agents. Traveler's diarrhoea (TD) occurs in 20 to 60% of European or North American travelers in intertropical areas [194]. The main agents are *E. coli* pathovars followed by enteroinvasive bacteria, enteric viruses, and protozoa (*G. intestinalis*, *C. parvum* and *E. histolytica*). Several studies have shown that a large proportion of travellers and immigrants from tropical and subtropical countries are affected by gastrointestinal disorders and harbour intestinal pathogens without clear gastrointestinal problems [195–200]. Travelling represents an important risk factor for acquiring infection also with spore-forming protozoa as *Cyclospora*, *Microsporidia*, and *Isospora* [201]. Protozoan infections with *G. lamblia* and *C. hominis*/*C. parvum* are the main nonviral causes of diarrhoea in industrialised countries [202] and are even more frequently seen as the cause of gastrointestinal complaints in returning travellers [196, 203, 204].

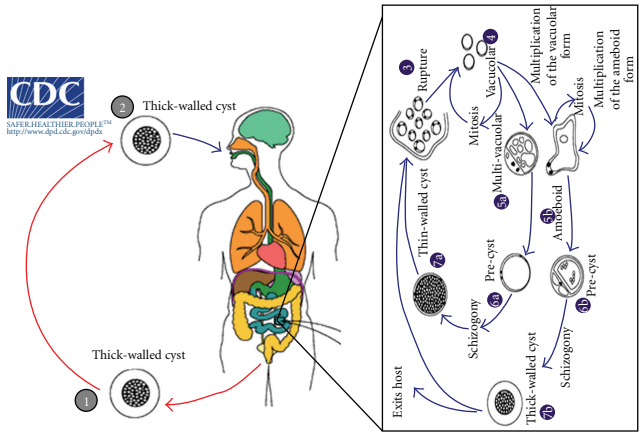
5.2. Principal World Regions Associated to Travel-Linked Transmission. An important study investigated the relationship between *Cyclospora* infection and seasonality in Turkey [205]. Parasites such as *Cryptosporidium*, *G. intestinalis*, *E. histolytica*/*dispar*, *B. hominis,* and others were also observed (Figure 6). The incidence of cyclosporiasis was higher in Summer and early Autumn and most of the *Cyclospora*-infected patients were without diarrhea. On the other hand, patients with a history of recent travel to a developing country in the tropics usually present persistent diarrhea. However, very mild infections may be underdiagnosed even if causing typical traveler's diarrhea. In a patient with a history of travel and persistent diarrhea unresponsive to the usual antibiotic and antidiarrhea treatment, stool studies for the cited protozoa infections should be always routinely performed (Table 1) (Figure 3).



(a) *Giardia* Life Cycle

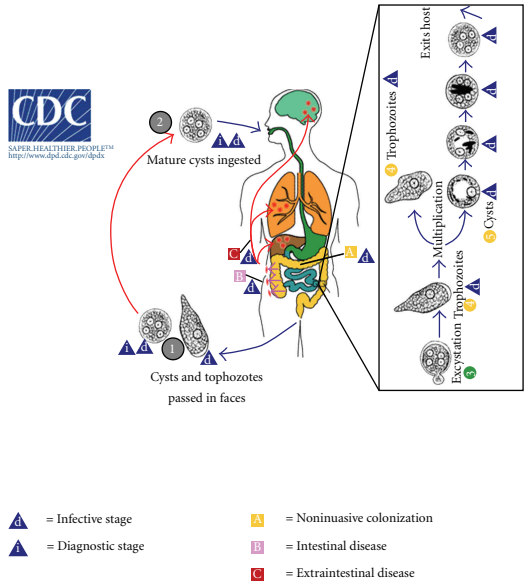


(b) *Cyclospora* Life Cycle



(c) *Blastocystis* Life Cycle

Figure 6: Continued.



(d) *Entamoeba* Life Cycle

Figure 6: *Schematic life cycle of the most recurrent Cryptosporidium coinfective and coemerging parasitic agents. Panel (a). Giardia intestinalis* (also called *Giardia lamblia* or *Giardia duodenalis*) is a flagellate parasite (Diplomonadida). Both cysts and trophozoites can be found in nondiarrheal feces (*diagnostic and infective stages*, (1)). Cysts are resistant forms and are responsible for transmission of giardiasis (*infective stage*, (2)). Infection occurs by the ingestion of water or food contaminated by cysts, or by the fecal-oral route (hands or fomites). In the small intestine, excystation releases trophozoites which multiply by longitudinal binary fission, remaining in the lumen of the proximal small bowel where they can be free or attached to the mucosa. Encystation occurs as the parasites transit toward the colon. *Panel (b). Cyclospora cayetanensis* is a coccidian parasite (Apicomplexa). When passed in stools, the oocyst is not infective (on the contrary of *Cryptosporidium*, thus direct fecal-oral transmission cannot occur). In the environment, sporulation occurs after days or weeks, resulting in division of the sporont into two sporocysts, each containing two sporozoites (*diagnostic and infective stages*, (1)). Fresh food and water can serve as vehicles for transmission and the sporulated oocysts are ingested (*infective stage*, (2)). The oocysts excyst in the gastrointestinal tract, freeing the sporozoites which invade the epithelial cells of the small intestine. Inside the cells they undergo asexual multiplication and sexual development to mature into oocysts, which will be shed in stools. *Panel (c). Blastocystis hominis* is a Heterokontid Chromista (Stramenopiles). The thick-walled cyst present in the stools (*diagnostic stage*, (1)), which varies tremendously in size from 6 to 40 μm, is believed to be responsible for external transmission, possibly by the fecal-oral route through ingestion of contaminated water or food (*infective stage*, (2)). The cysts infect epithelial cells of the digestive tract and multiply asexually. Vacuolar forms of the parasite give origin to multi vacuolar and ameboid forms. The multivacuolar form develops into a precyst that gives origin to a thin-walled cyst, thought to be responsible for autoinfection. The ameboid form gives origin to a precyst, which develops into thick-walled cyst by schizogony. The thick-walled cyst is excreted in feces. *Panel (d). Entamoeba histolytica/dispar* is an Amoebozoa parasite. Cysts and trophozoites are passed in feces (*diagnostic and infective stages*, (1)), the first found in formed, whereas the latest in diarrheal stool. Infection by *E. histolytica* occurs by ingestion of mature cysts in fecally contaminated food, water, or hands. Excystation occurs in the small intestine and trophozoites are released, which migrate to the large intestine and multiply by binary fission to produce cysts, where both stages are passed in the feces. Cysts can survive days to weeks in the external environment and are responsible for transmission (*diagnostic and infective stages*, (2)). Trophozoites passed in the stool are rapidly destroyed once outside the body, and if ingested would not survive exposure to the gastric environment. In many cases, the trophozoites remain confined to the intestinal lumen (*noninvasive infection*) of individuals who are asymptomatic carriers, passing cysts in their stool. In some patients the trophozoites invade the intestinal mucosa (*intestinal disease*), or, through the bloodstream, extraintestinal sites such as the liver, brain, and lungs (*extraintestinal disease*), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively, *E. histolytica* and *E. dispar*. These two species are morphologically indistinguishable unless *E. histolytica* is observed with ingested red blood cells (erythrophagocytosis). Infective and diagnostic stages, as well as body organs, are graphically reported, when surely assessed in the life cycle of the parasites. Modified from pictures available at the CDC site for parasite identification and diagnosis (http://www.dpd.cdc.gov/dpdx/HTML/Para_Health.htm). Putignani and Menchella, 2010.

A large study analysed 1,179 North-American travelers who visited Mexico from 2005 to 2007 [206]. TD was reported by 521 participants. A long stay in Mexico was identified as a risk factor for cryptosporidiosis. The Nassau County Health Department (NCHD) in Florida identified an outbreak of gastrointestinal (GI) illness in a returning choral group who toured Ireland in 2006 [207] (Table 4). In the long-term report performed in England and Wales from 2000 to 2003 [63] (Table 2), *C. hominis* was more prevalent in patients reporting recent foreign travel with late Summer and early Autumn picks [63] (Table 2). However, samples from other UK cases, contracted during foreign travels, were entirely characterised as *C. parvum* (type 1 and 2) [208] (Table 2). In the paper of Chalmers et al., 2008 [209], 115

isolates were investigated to assess UK transmission linked to travelling for *C. hominis*. Among the identified subtypes, the predominant was IbA10G2 (Table 2) not apparently linked to recent travel outside Europe [209].

5.3. Conclusions. Person travelling abroad, especially in regions identified as having high risk of infection (e.g., Ireland, UK, Turkey, Mexico) ought to undergo routine testing for intestinal parasites (Figure 4). A large variety of parasitic infections can be expected in homecoming travellers, and diagnostic procedures play a crucial role in the detection of intestinal parasites found in patients with and without gastrointestinal complaints. Although microscopy is considered the *gold standard*, it is labour intensive and its diagnostic performance critically depends on well-trained microscopists. Enzyme immunoassays [210, 211] and fluorescent antibody assays [212] have been accepted as alternative diagnostic methods for the detection of *G. lamblia* and *Cryptosporidium* in stools. Currently, the introduction of real-time PCR combining several targets into one multiplex assay offers the possibility of using DNA-based detection techniques in a high-throughput diagnostic approach [213].

6. Cryptosporidiosis in HIV-Infected Individuals

6.1. Infection Pathogenesis and Symptoms in HIV Impairment. The prevalence of cryptosporidiosis in HIV-infected patients with diarrhea has been reported to range from 3 to 16% in developed countries, depending on the population studied, degree of immunosuppression, and use of antiretroviral therapy although it is most frequent in men affected by gay-bowel syndrome [214, 215]. *C. parvum* is primarily responsible for watery diarrhoea, but it may also trigger biliary disease, hepatitis, pancreatitis, arthritis, and possibly respiratory tract infections [214, 216]. Diarrhoea is self-limited in immunocompetent individuals or in those whose CD4 cell counts >200/mm^3, but may be severe, and unremitting or relapsing in severely immunodeficient patients (CD4 cell counts <100/mm^3). In these cases chronic infection can lead to dehydration, malnutrition, malabsorption, wasting and, frequently, death [214]. Biliary cryptosporidiosis is more frequent in patients with CD4 cell counts <50/mm^3 and commonly presents with right upper quadrant pain, nausea, fever, vomiting and often with absence of diarrhea. Coinfection with cytomegalovirus or microsporidia has been frequently found in biliary cryptosporidiosis [216]. All segments of the gastrointestinal tract may be involved, but the small bowel is the main target organ followed by the colon [217]. Esophageal cryptosporidiosis, with parasites attached to the squamous mucosa and the luminal borders of submucosal glands and ducts, has been described both in adults and in children with AIDS [214]. Intestinal coinfection by *C. parvum* and *Cyclospora* species or cytomegalovirus is not rarely documented [216, 217] (Figure 6). Recent evidence suggests that epithelial apoptosis mediated by cytotoxic host T cells might play a role in the development of colonic lesions in AIDS-related cryptosporidiosis [218], suggesting a modified pathogenesis in HIV-positive patients. With the introduction of highly active antiretroviral therapy (HAART), the incidence of cryptosporidiosis has declined and chronic diarrhea and cryptosporidial infection often resolve with increases in CD4 lymphocyte count [219, 220]. In countries where HAART is available, HIV infection is generally a chronic disease strictly depending on the patient's adherence to treatment [221].

6.2. HIV-Related Cryptosporidiosis in Europe. Recently, in Europe few studies have traced the entire spectrum of epidemiological diffusion routes in HIV-infected patients. In a large study [222], *Cryptosporidium* isolates from HIV infected and uninfected patients from UK were compared to other isolates collected in different geographical areas (Kenya, Malawi, Brazil and Vietnam). Among the *C. parvum* group, strains clustered distinctly into either human or bovine genotypes regardless of the geographical origin, age, or HIV status of the patients (Table 2). The intragenotypic variation observed in the *C. parvum* human genotype was wide-ranging compared to that within the *C. parvum* bovine genotype group. The variation within genotypes was conserved in all geographical regions regardless of the patient HIV status (Table 2). Independent widespreading of genotypes was also observed in the study by Morgan et al., 2000 [223], where isolates from HIV infected patients from Switzerland were compared to other isolates from Kenya and the USA (Table 2). In Portugal, to investigate a possible zoonotic transmission in HIV-seropositive patients, isolates from patients, cattle, sheep and wild ruminants were collected from different regions and appeared largely limited to the only Portugal (Table 2) [78]. A surveillance study on *Cryptosporidium* in HIV-infected adults was carried out in Spain [224]. *C. hominis* was detected in 10 HIV-infected and C. *parvum* in six HIV-infected individuals showing a similar prevalence of the two species (Table 2).

6.2.1. HIV-Related Cryptosporidiosis in Italy. In Italy, during the previous decade, remarkable epidemiological and clinical studies have been provided [225–229] (Figure 5). An outbreak affected both HIV-positive and HIV-negative members of a drug rehabilitation community in 1995 in Northern Italy (Emilia Romagna) [226]. The 31% of the HIV-positive individuals were affected, with a severity grade according to CD4 cell count. The *Crytosporidium* oocysts were identified in the sediment of the water tanks used to store drinking water for the community, suggesting water as the vehicle of infection [226] (Figure 5).

However, following these pivotal studies, only a limited literature on AIDS-related cryptosporidiosis has been produced in the last ten years in Italy, clearly reflecting the positive impact of the HAART therapy on incidence and severity of opportunistic infections.

6.3. HIV-Related Cryptosporidiosis in USA and Canada. An unusual aspect of cryptosporidiosis onset in HIV/AIDS persons was approached by evaluating events of recreational water activities and risk of exposure to *Cryptosporidium* in

waterways of Baltimore (Maryland, USA) [230]. Interviews conducted on HIV/AIDS patients showed that approximately 48% of respondents participated in recreational water activities and had almost equally gender probability to contract waterborne pathogens.

6.4. HIV-Related Cryptosporidiosis in Africa. In Iran ten health centers were mapped for searching of *Cryptosporidium* in diarrheal patients. The study [231] showed that overall, 1.4% of all patients and 6.3% of diarrheal patients were infected by *Cryptosporidium* while AIDS patients who were suffering from diarrhea reached the 33.4%.

In Equatorial Guinea a study identified *C. parvum*, *C. hominis* and *C. meleagridis* in 35 cases: remarkably over 90% of the species were isolated from HIV-positive patients (Table 2) [232].

6.5. HIV-Related Cryptosporidiosis in Asia. A prevalence of intestinal parasites in HIV patients in India was determined by testing acute, chronic diarrhoea, and controls without diarrhoea [233]. *I. belli* was found in 18.6% of chronic diarrhoea and 7.3% of acute diarrhoea. *Cryptosporidium* was detected irrespective of specific clinical signs. Microsporidia and *C. cayetanensis* were detected only in one chronic case. Remarkably, *I. belli* appeared the predominant parasite associated with diarrhoea among HIV patients, providing an important evidence of a low-represented but emerging parasite in gastrointestinal infections [234]. Reports on the prevalence of cryptosporidial diarrhoea in HIV-infected adults from different parts of India from the mid-1990s have shown a range from 0.7 to 83% in symptomatic and from 1.4 to 57% in asymptomatic individuals, with very high rates in both groups and a strong correlation between immune status impairment and diversity of symptoms [235, 236]. In Taiwan the extremely low prevalence of intestinal cryptosporidiosis among HIV patients [76], despite detection of cryptosporidia in most of the surface waters [168], may be the result of using boiling water [5, 76]. In Malaysia, the commonness of fecal wastes from human and nonhuman hosts suggests that many environments, particularly water and soil, act as vehicles for the spreading of the disease [237]. A recent paper [238] investigated the occurrence of intestinal parasites in HIV/AIDS patients with chronic diarrhoea in Indonesia. Parasites were found in 84% of samples (single species infections, 71%; polyparasitism, 13%), with protozoan pathogens occurring most commonly. *Cryptosporidium*, *C. cayetanensis,* and *G. duodenalis* were the most frequent single infections. *Cryptosporidium* and *C. cayetanensis* occurred in 12% and 8% of all infections. The most common coinfection was with *B. hominis* and *Cryptosporidium* (6.3%) (Figure 6). No seasonal influence was observed for *Cryptosporidium*, *C. cayetanensis,* or *B. hominis*. A study [239], representing the first genetic identification of *Cryptosporidium* species in cattle in Thailand, showed that all HIV and cattle stool samples were characterize as *C. parvum*, suggesting a possible zoonotic transmission for HIV individuals (Table 2) [239].

6.6. HIV-Related Cryptosporidiosis in South and Central America. In Perù, a study on the genetic diversity of *Cryptosporidium* spp. in HIV-positive people [240] suggested that *C. hominis* is the predominant species in HIV patients, while zoonotic *Cryptosporidium* spp. accounts for about 30% of cases (Table 2) [240]. A prospective longitudinal cohort study [241] conducted in Haiti showed that AIDS patients were infected by either human or animal genotypes. These data confirm that immunocompromised individuals are susceptible to a wide range of *Cryptosporidium* spp. which remains a frequent hazard especially in countries with poor hygiene and overcrowded conditions associated with urban slums [69].

6.7. Conclusions. In developing countries with no or limited access to HAART, AIDS is rapidly expanding with a high fatality ratio (Figure 4). Furthermore, new HAART baselines, where introduced, are now modifying HIV circulation modes and opportunistic infections in these geographic areas. The data on the parasite's transmission in the Sub-Saharan Africa clearly show high rates of severe or even fatal *Cryptosporidium* infections, massively contributing to the entire worldwide burden of sporadic cases (Figure 4). In HIV patients the impact of *C. felis* infection in tropical countries is becoming an emerging issue. In developed countries (Figure 4), therapeutic approaches are effective in reducing fecal output, but the eradication of the parasite is rarely obtained. Cryptosporidiosis is still a leading opportunistic infection in HIV persons and, despite HAART therapy, it should not be underestimated in epidemiological tracing and clinical followup of these patients. Immunocompromised persons should be cautioned on the potential risks from recreational water contact and their water-related practices should always be considered in the clinical monitoring of their health status.

7. Cryptosporidiosis in Children

7.1. General Notes. In the early 1980s, diarrhoeal disorders were the biggest child killers, responsible for an estimated 4.6 million deaths worldwide every year. Despite widespread use of oral rehydration therapies and an increased understanding of the pathogenesis of diarrhoea, 2.5 million children still die from these illnesses every year, almost all of them in developing countries [242]. Parasites such as *Cryptosporidium* and *Giardia* are leading agents of chronic or persistent diarrhoea worsened by specific risk factors such as malnutrition or immune deficiency [243].

7.2. Children Cryptosporidiosis in Europe. Studies on cryptosporidiosis in children have been progressively developed in the last few years in Europe [35, 244]. Survey laboratory practices in the UK have recently included screening of all fecal specimens from children aged 15 or younger, with routine reports to the *Communicable Disease Surveillance Centre* (CDSC) of the PHLS (*Public Health Laboratory Service*) (Table 3) [245]. Among the described outbreaks (see Sections 3.1 and 3.2), in many episodes the children represented the largest portion of confirmed cases of cryptosporidiosis

[84, 246–251] (Table 4). The work by Chalmers et al., 2009 [63] showed that the epidemiology of human cryptosporidiosis in UK, from 2000 to 2003, importantly differed among *Cryptosporidium* infecting species with reference to children age groups (Table 1) (Figure 3). The mean age of *C. parvum* cases was lower than that of *C. hominis* cases. However, an opposite trend in infants under one year, independently from the gender and possibly linked to the stay of the babies in day-care nurseries, was observed. A seasonal distribution of cryptosporidiosis in children in a region of North-Eastern Spain, was determined [53] (see Introduction, Section 1.3.2). Prevalence was highest in children aged 1 to 3 years old and significantly more elevated in the Autumn–Winter period than in the Spring-Summer period [53]. Furthermore, the stay within a nursery and the improper diaper usage, for a group of 24 day-care children, were analysed as triggering factors in the community outbreak described by Ortega et al. in 2006 in Spain [252] (Table 4). In Spring 1998, an acute gastroenteritis outbreak, which mainly affected preschool children, took place in Guadarrama (Spain) (Table 4) [253]. In Spain a large surveillance study on a set of stool samples collected from *Cryptosporidium*-infected patients, including 92 children [224], revealed a high heterogenicity of species (Table 2). A recent study [254] performed, amongst the others, on 32 hospitalised children, revealed an impairment-dependant prevalence of *Cryptosporidium* species in hospitalised children [254] (Table 2). Large-scale surveys of representative population groups in the Central and North-Western regions of the Russian Federation showed a mean population incidence of 3.3%, much higher in children (3.7%) than in adults (0.4%). There were differences in the infection rates between genders (boys more affected than girls) but not between rural and urban children [255].

7.2.1. Children Cryptosporidiosis in Italy. A large group of 618 children with diarrhea was prospectively evaluated for viral, bacterial, and parasitic enteric pathogens in a multicenter study performed by the *Italian Study Group on Gastrointestinal Infections* [256] (Figure 5). The agents mainly associated with disease were Rotavirus, *Salmonella,* and *Campylobacter*. *Cryptosporidium* and *Giardia* were observed only in 10 patients [256].

Another important study [257] evaluated the prevalence of *C. parvum* in 368 hospitalized children with enteritis, of whom 359 were immunocompetent and 9 were HIV-infected. *C. parvum* oocysts were found in seven out of 368 specimens. All subjects with cryptosporidiosis were living in Apulia (South Italy) and had not travelled outside of Italy. No differences between those living in urban or rural areas was observed and no correlation was found between seasonal timing of specimen collection and positivity for *C. parvum*. Importantly, the areas were served by chlorinated water systems. In two out of seven children the parasite was associated also with *S. typhimurium* in one case and *Rotavirus* spp. in the other. The population study on the drug community members [226], included the subset of their 135 children. Interestingly, 28 out of 135 children, aged in the range 0–12 years, were affected by *Cryptosporidium*. Updated data on cryptosporidosis prevalence in pediatric population are nowadays missing, despite the growing clinical interest on children cryptosporidiosis.

7.3. Children Cryptosporidiosis in USA and Canada. In 2007 the Idaho waterborne outbreak in a municipal park [258] (Table 4) affected, over 50 ill people, 36 children with a peak ranging in the 4–6 age group. In 2006, in a waterborne outbreak the 83% of primary cases occurred in children [85] (Table 4). Also in the waterborne outbreak registered in Illinois in 2001, children were predominantly involved [259]. Interestingly, *C. hominis* was the only etiological agent and one of the risk agents was the heavy usage of recreational water by diaper-aged children (Figure 3) (Table 4). Also in the outbreak registered in Florida in 1999 [260] (Table 4), over the 86 park visitors interviewed, the 38 which had gastroenteritis were 8 year old over an age range of 2–65 years. During an outbreak of giardiasis and cryptosporidiosis in Central Florida in September 2006, including also coinfection (Figure 6), only children were affected [261] (Table 4).

Currently, the number of internationally adopted children worldwide has rapidly increased during the past decade, providing an additional surveillance indicator for cryptosporidiosis acquired in their country of origin. The work of Saiman [195] performed a retrospective cohort study on 504 children adopted from abroad in the USA from 1997 to 1998 to determine the prevalence of infectious diseases. Being born in Eastern Europe was a risk factor for the acquisition of *G. lamblia*. Thirty-two children had one or more organisms identified by stool microscopy: *B. hominis*, *Dientamoeba fragilis*, *E. nana*, *Hymenolepis nana*, *Ascaris lumbricoides*, *Chilomastix mesnili*, and *Entamoeba hartmanni* were detected. C*ryptosporidium* species were identified only in four out of 504 children, but probably underestimated for the low sensitivity of the direct fluorescent method.

7.4. Children Cryptosporidiosis in New Zealand and Australia. An outbreak affecting eight children in Australia was associated to a contamination of drinking unpasteurised milk [262] (Table 4). Despite being rarely observed, a pivotal work [263] described a previous children outbreak of cryptosporidiosis linked to drinking school milk in September 1995 in the UK. The only exposure significantly associated with illness was drinking school milk, possibly infected by a temporarily failing pasteurisation plant at the local producing farm. A children community outbreak was also reported in New Zealand in 2001 [264] (Table 4). The 19 cases aged under 7 years, were linked to a specific farm event identified as parasite hand-to-mouth transfer after touching an infected calf.

7.5. Children Cryptosporidiosis in Africa. C. parvum is a leading pathogen in children in African developing countries. Here, as in other low-income areas, with no or limited access to HAART, AIDS is rapidly expanding in infants [265]. The fatality rate increased due to opportunistic infections, with *C. parvum* being one of the leading agents

of severe diarrhea in infants affected by HIV/AIDS [265]. However, stunting is a major burden in developing countries, affecting ~147 million children. Repeated or prolonged episodes of diarrhoea during childhood increase the risk of stunting, which is believed to be associated with significant morbidity. Although the relationships between malnutrition, environmental and diarrhoeal illnesses are complex, studies have suggested a connection between stunting and diarrhoea causing pathogens, including *G. lamblia*, *C. parvum,* and enteroaggregative *E. coli* (EAggEC) [266]. A recent paper [267], showed that the microsporidian parasite *E. bieneusi* is associated with lower rates of weight gain in children with persistent diarrhea in Uganda. Children with microsporidiosis were predicted to weigh 1.3 kg less than children without microsporidiosis at 5 years of age [267]. The benefits of exclusive breastfeeding for health in infants have been widely described. The study by Bilenko et al., 2008 [126], considered whether partial breastfeeding has protective effects against enteric infection and associated morbidity in population where early addition of supplementation is common. In this study, 238 Bedouin infants were followed from birth to 18 months. Exclusive breastfeeding was protective against infection and morbidity at ages 0 to 3 months. In the age range of 4 to 6 months, partial versus nonbreastfeeding was associated with lower rates of infection with *Cryptosporidium* spp. and *Campylobacter* spp. In older children (10–12 month age range) partial breastfeeding as compared to none, protected against infections with *Cryptosporidium* spp. and *G. lamblia*. Short-term protection from maternal antibodies passed to infants during breastfeeding may result in a lack of cryptosporidial infection in infancy. This protection of breastfeeding children may, however, result in such children developing less anti-*Cryptosporidium* immunity of their own, so that, by school age, the children who had been breastfed are those most likely to be found infected [268]. Hospital- and community-based studies in Sub-Saharan Africa document a high prevalence of cryptosporidiosis in children aged 6–36 months, particularly among those who are malnourished or HIV-positive and during rainy seasons. Transmission appears to occur predominantly through an anthroponotic cycle [269]. Prevalence of *Cryptosporidium* and *Giardia* infections was assessed among children using protected and unprotected water sources in Eastern Ethiopia, in November 2005 to May 2006 [270]. Of 655 children examined, 80 were infected with *Cryptosporidium* and 231 with *Giardia*. No difference was observed in the prevalence of cryptosporidiosis and giardiasis between children drinking water from protected and unprotected sources [270]. The study of Dlamini et al., 2005 [271], reports the first finding on *Cryptosporidium* spp. detection among children of the Swazi ethnic group in Zimbabwe. A study focused on the prevalence of cryptosporidiosis in pediatric hospital patients in Niger [272], where malnutrition and diarrhoea are two major public health issues. The aim of this study was to get a first evaluation on the prevalence of *Cryptosporidium* spp. in the stools of hospitalized children younger than 5 years of age. The weight/age ratio to describe malnutrition was calculated and analyzed with the *Epi-Info* software [273, 274], (Table 3). In the three months study 220 children were included (mean age 20 months) showing that 65% of the children were suffering from moderate and severe malnutrition. Diarrhoea was reported in 52% of the children. *Cryptosporidium* oocysts were detected in 12 out of 220 children with 10 children malnourished. A study on children (median age 13.5 months) presenting with acute diarrhea and rehydration clinics in Madagascar, was undertaken between May 2004–May 2005 [275]. Twelve cases of cryptosporidiosis were detected only in the rainy season. As 11 of the 12 cases were caused by *C. hominis* and only one by *C. parvum*, most of the cases were probably the result of anthroponotic transmission (Table 4) [275]. A large study was performed in Kuwait to investigate the incidence of cryptosporidial infection in children presenting with gastrointestinal symptoms at the local hospitals [54]. Over a period of three years, fecal samples from 3549 children were analyzed for the presence of *Cryptosporidium* oocysts, detected in 51 children with diarrhea. Prevalence was highest in children older than two years of age. The maximum number of cases was seen during the months January to April, indicating a marked seasonal variation. Three possible modes of infection transmission were inferred: (i) drinking contaminated water stored in overhead water tanks; (ii) person to person; (iii) contact with infected animals. A common polyparasitism was mainly due to the recurrent *Cryptosporidium* co-infective *Giardia* and *Cyclospora* parasites, as also reported by recent outbreak reports [261, 276, 277] (Table 4), confirming these parasites as largely emerging pathogens [1, 201] also with *B. hominis* and *E. histolytica*/*dispar* [278] (Figure 6).

7.6. Children Cryptosporidiosis in Asia. An interesting correlation between subtypes distribution and geographical settings for children infections, was investigated to identify geographical-dependent variation [36] (Table 2). In this study, species, genotypes, and subgenotypes of *Cryptosporidium* spp. infections were identified for the first time in a well-defined cohort of children in Southern India. Only one previous report was produced on genotypes distribution of *Cryptosporidium* spp. in children in Eastern India [57]. *C. parvum*-positive samples revealed that all were subgenotype Ic, usually associated with anthroponotic transmission (Table 2). There were no significant differences in demographic or clinical (nutritional status, vomiting, fever) characteristics between *C. hominis* and *C. parvum* or *C. felis* [87] infected children and those infected with different subgenotypes. However, *C. hominis*-infected children had a significantly greater severity of diarrhea [36]. There was also a trend toward a longer average duration of diarrhea in *C. hominis*-infected children than in those infected with other species (Table 1) (Figure 3). There were two significant time clusters of cryptosporidial diarrhea, one during February-March and the other during June–August. In the other study of Ajjampur [235], fecal samples from 158 children with and 99 children without diarrhoea were tested for enteric pathogens in Southern India. Remarkably, *Cryptosporidium* spp. resulted in one of the most common causes of diarrhoea in hospitalized children [235, 236].

The epidemiology, clinical features, nutritional status, and causative agents of diarrhea were studied in 289 children in Bangladesh [279]. Compared with malnourished and/or stunted children, better-nourished children experienced significantly fewer diarrheal episodes. *G. lamblia*, *C. parvum*, and *E. histolytica* were the most common protozoan agents. A very recent study [280] performed in Bangladesh, examined whether malnutrition, may increase the risk of diarrhea equally for all enteropathogens in infants. Two hundred eighty-nine Bangladeshi children, 2 to 5 years of age, were included in the study. Malnutrition was present in 39% of the children. Of the identified enteropathogens from stool samples, only enterotoxigenic *E. coli*, *Cryptosporidium* spp., and *E. histolytica* were significantly more prevalent in malnourished children, suggesting that malnutrition may represent a differential risk for enteric pathogens associated with diarrheal illness. A study [281] was conducted to investigate the presence of intestinal parasites among 475 preschool children (aged 3 months to 5 years) in Thailand. The most frequent parasites identified were *G. lamblia* and *Cryptosporidium* spp. Highest proportion of intestinal parasites occurred during the rainy season (June–October). A 5-year hospital-based retrospective analysis was aimed to find out the intestinal protozoal parasitic profile in 1790 preschool and school-age children visiting the hospital with gastrointestinal illness in Nepal [282]. *G. lamblia* was the most prevalent pathogenic protozoan intestinal parasite, followed by *E. histolytica*. Interestingly, opportunistic pathogens like *C. cayetanensis* and *Cryptosporidium* spp. were detected in immunocompromised children below two years of age as a result of vertical transmission, which is alarming for a country like Nepal presenting a "*concentrated epidemic*" HIV infection period [282]. Intestinal parasites are still a major health problem in Turkey. The study of Börekçı and Uzel [283] identified one or more parasites in 43% of the children. *G. intestinalis* was found to be the most common parasite, followed by *E. histolytica* plus *E. coli*, *E. coli*, *E. nana*, and *Cryptosporidium* spp. In Turkey, the first waterborne outbreak of cryptosporidiosis with *Cyclospora* coinfection mainly affected children aged between 0 and 14 years [276] (Table 4) (Figure 6). An interesting topic for children infections in an Asian high-income country, was discussed by Matsubayashi et al., 2005, on *Cryptosporidium* and *Giardia* transmission in a zoo in Japan [284]. *Cryptosporidium* spp. was found only in a raccoon dog, and *Giardia* spp. was detected in a mandarin duck and two ruddy shelducks. These results corroborate the idea that infected animals could serve as a direct source of contamination for children. In a recent compendium [285], recommendations for public health officials, veterinarians, animal venue staff members and exhibitors, visitors to animal venues, and physicians have been provided. Pet and wild animal transmission has been more critically revised as an important reservoir for cryptosporidiosis in children [78, 118, 284, 286].

7.7. Children Cryptosporidiosis in South and Central America. In South America, cryptosporidiosis is often observed as a pediatric disease in areas where *Cryptosporidium* spp. are endemic (e.g., Perù). Children < two years of age are frequently infected in community and hospital settings. The spectrum of symptoms is diverse, ranging from acute, severe chronic diarrhea, or vomiting to asymptomatic infections. In a community-based study in Perù, about 30% of immunocompetent children with cryptosporidiosis reported diarrhea [50]. This four-year study was fundamental for size of sampling set (533 children enrolled), age of children (median age corresponding to 14 days), number of stool specimens (44,042), and *Cryptosporidium* species identified (Table 2). Children infected with *C. hominis* had higher parasite excretion scores [287] than those infected with other species of *Cryptosporidium*. Associated clinical manifestations at first infection varied among different *Cryptosporidium* spp. and genotypes (Table 2). In general, distribution of species was similar to that found in a previous study on Peruvian HIV population [288], where all *C. parvum* specimens were described to belong to subtype family IIc [87]. In Haiti, the study by Raccurt et al. 2006 [69], highlighted the water contamination in urban slum conditions as a major risk of cryptosporidiosis in children. The considered risk factors, including age at first infection, hygiene parameters, presence of animals, house infrastructure, and indirect economic indicators did not provide statistically significant correlation to *Cryptosporidium* spp. or subtype families and, therefore, were not identified as risk factors, apparently in contrast to transmission of *Cryptosporidium* spp. in industrialized nations. A seroepidemiologic study [289] was conducted in Guatemala to determine the feasibility of using antibody markers as indicators of waterborne pathogen infection in rural areas of this country. The prevalence of antibodies was lowest in children 6–12 months old compared with the older age groups (up to 36 months) but still detectable, providing a useful screening tool for the main waterborne pathogens [289]. Such an approach may provide a suitable tool for determining the prevalence of infection in very young children. Molecular characterisation of *Cryptosporidium* infections among Cuban children (aged 2–8 years) with diarrhoea, were described by Pelayo et al., 2008 [268]. In this study, in contrast with a previous report on intestinal coccidia in Cuban pediatric patients [290], differences in symptoms were detected, possibly age-related.

7.8. Conclusions. Infectious diarrheal diseases remain an important cause of childhood morbidity in developed countries. The recent confirmation of an infection route of *Cryptosporidium* linked to drinking unpasteurised milk highlights the need to evaluate the entire transmission variety of the parasite, besides the already well-known and identified classical courses of disease in children. In pediatric populations, prevalence data are still underestimated, due to a poor clinical valuation of pathognomic symptoms and to the absence of advanced laboratory tools in diagnostic routine panels. Literature regarding developing countries shows that anthroponotic transmission is the principal mode of infection in children population, while less representative are the water or environmental sources contaminated with zoonotic *Cryptosporidium* genotypes, a direct

contact with animals or the presence within farms and/or associated waters. Interestingly, of the 71 *Cryptosporidium*-linked outbreaks (Table 4), 17 outbreaks (23.9%), defined as community-linked, appear to involve predominantly children, underlying the person-to-person contact as the prevailing transmission route. Geographically, this type of outbreaks seem to be concentrated in the USA and in the UK but have been also mapped in New Zealand and South-America (Table 3) (Figure 4). The high heterogenicity of *C. hominis* genotypes, notified in many developing areas for childhood, represents an indicator of endemicity for the transmission of cryptosporidiosis (Figure 4). In the poorest areas, gastrointestinal parasitosis, enhanced by malnutrition, play a major role in children with severe immune impairment, with *C. hominis* being the leading agent of severe diarrhea. Intestinal dysfunction contributes to growth failure and further immune derangement, leading to wasting, and significantly enhancing children mortality. New areas of research on the relationship between breastfeeding and onset/progression of the cryptosporidiosis should be explored, especially in children population characterised by paucity of hygiene, nutrition and hydration, particularly in the first months of life. Lastly, the growing number of internationally adopted children requires an appropriate surveillance to ensure the long-term health of adopted children as well as their families. Thus, periodic surveys of large cohorts of internationally adopted children are now essential to monitor global changing epidemiologic trends.

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