Cryptosporidiosis in HIV-positive patients and related risk factors: A systematic review and meta-analysis

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Received 1 October 2019, Accepted 9 April 2020, Published online 29 April 2020

Abstract – Cryptosporidium is one of the major causes of diarrhea in HIV-positive patients. The aim of this study is to systematically review and meta-analyze the prevalence of Cryptosporidium in these patients. PubMed, Science Direct, Google Scholar, Web of Science, Cochrane and Ovid databases were searched for relevant studies dating from the period of 1 January 2000 to 31 December 2017. Data extraction for the included studies was performed independently by two authors. The overall pooled prevalence was calculated and subgroup analysis was performed on diagnostic methods, geographical distribution and study population. Meta-regression for the included studies was performed on the year of publication, proportion of patients with diarrhea, and proportion of patients with CD4 < 200 cells/mL. One hundred and sixty-one studies and 51,123 HIV-positive participants were included. The overall pooled prevalence of Cryptosporidium infection in HIV-positive patients was 11.2% (CI95%: 9.4%–13.0%). The pooled prevalence was estimated to be 10.0% (CI95%: 8.4%–11.8%) using staining methods, 13.5% (CI95%: 8.9%–19.8%) using molecular methods, and 26.3% (CI95%: 15.0%–42.0%) using antigen detection methods. The prevalence of Cryptosporidium in HIV patients was significantly associated with the country of study. Also, there were statistical differences between the diarrhea, CD4 < 200 cells/mL, and antiretroviral therapy risk factors with Cryptosporidiosis. Thus, Cryptosporidium is a common infection in HIV-positive patients, and safe water and hand-hygiene should be implemented to prevent cryptosporidiosis occurrence in these patients.

Key words: Cryptosporidium infection, HIV, AIDS, Systematic review.

Résumé – Cryptosporidiose chez les patients VIH-séropositifs et facteurs de risque associés : revue systématique et méta-analyse. Cryptosporidium est l’une des principales causes de diarrhée chez les patients séropositifs pour le VIH. Le but de cette étude est de revoir et méta-analyser systématiquement la prévalence de Cryptosporidium chez ces patients. Les bases de données PubMed, Science Direct, Google Scholar, Web of Science, Cochrane et Ovid ont été recherchées pour des études pertinentes datant du 1er janvier 2000 au 31 décembre 2017. L’extraction des données pour les études incluses a été réalisée indépendamment par deux auteurs. La prévalence globale combinée a été calculée et une analyse en sous-groupes a été effectuée sur les méthodes de...
Introduction

Cryptosporidium is an intracellular protozoan parasite that infects the gastrointestinal epithelium of a wide range of animals as well as humans, and causes diarrheal disease [29, 103]. Among the 38 species of Cryptosporidium currently recognized, Cryptosporidium hominis and Cryptosporidium parvum are responsible for the majority of human infections [43]. However, other species including C. meleagris, C. canis, C. felis, and C. muris have been identified in immunocompromized patients [178]. Transmission of the infection is most common by the fecal-oral route, via the consumption of contaminated water and food, and contact with infected persons or animals [29]. Infection in immunocompetent patients is either asymptomatic or presents with profuse acute or persistent watery diarrhea, nausea and vomiting, stomach cramps, and occasionally fever that lasts approximately 2 weeks. However, in patients with immune deficiencies, the infection might cause prolonged symptoms and lead to chronic diarrhea that lasts more than 2 months, or fulminant diarrhea with more than 2 L of watery stools per day [29].

It is estimated that in 2016, 36.7 million people were infected with HIV worldwide. During the onset of the AIDS epidemic in the early 1980s Cryptosporidium became widely recognized as a human pathogen [160]. Diarrhea is a common problem in AIDS patients and about 30%–60% of patients in developed countries and 90% in developing countries experience diarrhea [44]. Diarrhea significantly influences quality of life and can lead to complications such as dehydration, malnutrition, weight loss and even death [101]. Cryptosporidiosis was considered one of the original AIDS-defining illnesses and a major risk factor for mortality compared to other AIDS-defining illnesses [32]. The prevalence of Cryptosporidium in immunocompetent patients varies widely, ranging from 0% to 10%, depending on country socioeconomic status [28]. Several studies have investigated the prevalence of Cryptosporidium in HIV-positive patients and have reported a wide range of estimates in different settings.

The aim of the study was to systematically review and meta-analyze the worldwide prevalence and geographic distribution of Cryptosporidium in HIV-positive patients and to compare the estimated prevalence using different diagnostic methods.

Methods

Search strategy and study selection

We performed this systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [87]. PubMed, Science Direct, Google Scholar, Web of Science, Cochrane and Ovid databases were searched from 1 January 2000 to 31 December 2017 restricted to the English language using the following keywords: “Cryptosporidium”, “cryptosporidiosis”, “HIV”, “immunodeficiency”, “acquired immune deficiency syndrome”, or “AIDS”. After removing duplicate records, two authors independently reviewed the titles and/or abstracts of all records identified by the search. Full-texts were retrieved and evaluated for potentially relevant studies. All disagreements were resolved by consensus.

Inclusion and exclusion criteria

Studies were included in the systematic review and meta-analysis if the study was performed on HIV/AIDS patients with or without diarrhea and the prevalence of Cryptosporidium was evaluated using staining, antigen detection or molecular methods. Conference abstracts, animal studies, case reports, comments, and reviews were excluded. When duplicate reports of the same research were suspected, the paper reporting more relevant data was included.

Data extraction

Data extraction was performed independently by two authors and the following information was extracted: first author, year of publication, country of study, average level of income in the country of study, region of study, study design, number of HIV/AIDS participants, sex ratio of participants, mean age, diagnostic methods, number of participants co-infected with Cryptosporidium, number of participants with CD4 counts < 200 cell/mm³, and number of participants with diarrhea. The region of study was determined according to the WHO Global Burden of Disease Regions [176]. The level of income was retrieved from the 2017 World Bank classification of countries by income [175].
Meta-analysis

Comprehensive meta-analysis 2.2 (Biostat Inc., USA) was used to calculate the pooled prevalence using a random-effects model. Heterogeneity was assessed using the $I^2$ index and Cochran-Q test. An $I^2$ index $>70\%$ or a significant Cochran-Q test indicated heterogeneity [37]. Also, publication bias was assessed using Egger’s intercept and visual inspection of the funnel plot. Univariate analysis was performed on the following risk factors and variables: diagnostic method, country of study, average level of income in the country of study, region of study, number of participants $>100$, proportion of patients with diarrhea, and proportion of patients with low CD4 counts. Meta-regression was performed using the method of moments on the following variables: year of publication, the proportion of patients with diarrhea, and proportion of patients with low CD4 counts.

In all analyses, if a study used multiple diagnostic methods, we preferred the prevalence estimated using molecular methods to the other two, and staining methods to antigen detection methods. This procedure was implemented for all analyses except in the subgroup analysis of diagnostic methods. In these studies, all estimates of prevalence using different diagnostic methods were included. Publication bias was assessed using Egger’s regression and visual inspection of the Funnel plot. A significant Egger’s regression and an asymmetric Funnel plot indicated publication bias [37]. The level of significance for all tests was $p < 0.05$.

Results

Search results

After removing duplicates, titles and/or abstracts of 1986 records retrieved by the search were screened and 237 studies were selected to be reviewed in more detail using their full-texts. Of these, 161 studies fit the inclusion criteria and were included in the systematic review and meta-analysis (Fig. 1).
Characteristics of studies

A total of 51,123 HIV/AIDS patients participated in these studies of which 5408 patients were co-infected with Cryptosporidium. The overall male to female ratio was 61.2% to 38.8% (M:F = 1.58:1) among all participants and 67.2% to 32.8% (M:F = 2.08:1) among infected participants. The mean age of participants in the included studies was 33.9 years (ranged from 10 months to 45 years). In total, studies from 40 countries worldwide were included. The countries with the most included studies were India (25%, 41/161), Ethiopia (11%, 18/161), Brazil (8%, 12/161), Nigeria and Iran (6%, 10/161). More than 40% of studies were performed in lower-middle-income countries (68/161), followed by upper-middle-income countries (32%, 52/161), low-income countries (20%, 33/161) and only 5% were performed in high-income countries (8/161). Studies were also categorized based on the WHO Global Burden of Disease Regions (Table 1). Among these studies, meta-analysis showed that the proportion of participants with diarrhea and CD4 counts < 200 cells/mL significantly correlated with the pooled prevalence (p < 0.0001). Similarly, the proportion of participants who received ART significantly correlated with the pooled prevalence (p < 0.0001) (Table 3). Our study indicated that having diarrhea and having less than 200 CD4 cells µL in HIV-infected patients, increase the risk of infection by Cryptosporidium, whereas using antiretroviral therapy in HIV-infected patients meaningfully decreases the risk of cryptosporidiosis. The funnel plot showing an asymmetric plot with studies missing on the right side and a statistically significant Egger's regression suggest the possibility of publication bias (Fig. 6).

Discussion

Diarrhea caused by opportunistic intestinal protozoa is a common problem in HIV-infected patients. With a total number of 36 million HIV-infected patients and 11.2% prevalence of Cryptosporidium co-infection with HIV, approximately 4 million HIV patients are estimated to be infected with Cryptosporidium worldwide. The present meta-analysis of 161 studies published from 2000 to 2017 on the topic of Cryptosporidium infections in patients with HIV shows that the pooled worldwide prevalence of Cryptosporidium in patients with HIV is 14.4%. A systematic review previously assessed the worldwide prevalence of Cryptosporidium among patients with HIV, but did not establish the risk factors [170]. The prevalence of Cryptosporidium in the immunocompetent population has been estimated to be not more than 1% in high-income and 5%–10% in low-income countries [28]. In a case-control study, it was shown that HIV-positive patients had a 20-fold risk of becoming infected with Cryptosporidium [97, 98]. Therefore, in addition to a greater risk of developing symptomatic disease and having more severe and prolonged symptoms, patients with HIV have a greater risk of infection with Cryptosporidium [60].

Several mechanisms have been suggested to explain the susceptibility of AIDS patients to cryptosporidiosis. CD4 cells play a major role in the immune response to gastrointestinal pathogens, and it has been shown that low CD4 counts are associated with increased risk of infection with enteric parasites and chronic diarrhea [104]. Due to immunosuppression, symptoms of cryptosporidiosis in patients with AIDS are expressed differently in terms of severity, duration, and responses to drug treatment. It has been shown that there is a significant relationship between increased mortality rates and cryptosporidiosis in AIDS patients [19, 179]. Similarly, in the present meta-analysis,
Table 1. Baseline characteristics of the included studies.

| Paper ID | First author | Year | Country/State | Number of participants | Number infected | Diagnostic method | Patients with diarrhea | Patients with CD4<200 |
|----------|--------------|------|---------------|------------------------|----------------|---------------------|------------------------|-----------------------|
| 1        | Inungu J     | 2000 | Louisiana     | 6913                   | 239            | Staining           | NR                     | NR                    |
| 2        | Chokephaibulkit K | 2001 | Thailand     | 82                      | 7              | Ziehl-Neelsen       | 100.00%                | NR                    |
| 3        | Gassama A    | 2001 | Senegal       | 318                     | 15             | Ziehl-Neelsen       | 49.70%                 | NR                    |
| 4        | Lebbad M     | 2001 | Guinea-Bissau | 37                      | 9              | Ziehl-Neelsen       | NR                     | NR                    |
| 5        | Wiwanitkit V | 2001 | Thailand     | 60                      | 2              | Odine and Modified  | Trichromes             | 46.70%                | 41.70%                |
| 6        | Brink AK     | 2002 | Uganda       | 358                     | 18             | Ziehl-Neelsen       | 70.10%                 | NR                    |
| 7        | Joshi M      | 2002 | India        | 94                      | 8              | Ziehl-Neelsen       | NR                     | NR                    |
| 8        | Kumar SS     | 2002 | India        | 150                     | 14             | Ziehl-Neelsen       | 66.70%                 | NR                    |
| 9        | Leav BA      | 2002 | Congo        | 101                     | 25             | Ziehl-Neelsen       | NR                     | NR                    |
| 10       | Mohandas K   | 2002 | India        | 120                     | 13             | Ziehl-Neelsen       | 67.50%                 | NR                    |
| 11       | Sakarisiamant W | 2002 | Thailand    | 156                     | 20             | Ziehl-Nelson        | NR                     | NR                    |
| 12       | Wanachiwanawin D | 2002 | Thailand    | 95                      | 3              | Ziehl-Neelsen       | 100.00%                | NR                    |
| 13       | Adeji A      | 2003 | Ghana        | 21                      | 6              | Ziehl-Neelsen       | 100.00%                | NR                    |
| 14       | Arenas-Pinto A | 2003 | Venezuela   | 304                     | 45             | Ziehl-Neelsen       | 71.40%                 | NR                    |
| 15       | Cama VA      | 2003 | Peru         | 2672                    | 354            | Ziehl-Neelsen       | NR                     | NR                    |
| 16       | Cranendonk R | 2003 | Malawi       | 348                     | 16             | Phenol-auramine-O-  | fluorescence           | 49.80%                | NR                    |
| 17       | Shenoy S     | 2003 | India        | 120                     | 21             | Ziehl-Neelsen       | 100.00%                | NR                    |
| 18       | Silva CV     | 2003 | Brazil       | 52                      | 3              | Safranin/Methylene | NR                     | NR                    |
| 19       | Singh A      | 2003 | India        | 100                     | 47             | Ziehl-Neelsen       | NR                     | NR                    |
| 20       | Carcamo C    | 2004 | Peru         | 294                     | 39             | Modified Safranin  | 50.00%                 | NR                    |
| 21       | Ribiero PC   | 2004 | Brazil       | 75                      | 7              | Safranin/Methylene | NR                     | NR                    |
| 22       | Zali MR      | 2004 | Iran         | 206                     | 3              | Ziehl-Neelsen       | 13.60%                 | NR                    |
| 23       | Certad G     | 2005 | Venezuela    | 397                     | 59             | Ziehl-Neelsen       | 75.60%                 | NR                    |
| 24       | Guk SM       | 2005 | Korea        | 67                      | 7              | Ziehl-Neelsen       | NR                     | NR                    |
| 25       | Houpt ER     | 2005 | Tanzania     | 127                     | 22             | IFA                 | 48.00%                 | NR                    |
| 26       | Lim YA       | 2005 | Malaysia     | 66                      | 2              | Ziehl-Neelsen       | 9.10%                  | NR                    |
| 27       | Marques FR   | 2005 | Brazil       | 94                      | 8              | Ziehl-Neelsen, ELISA  | NR                     | NR                    |
| 28       | Pinlaor S    | 2005 | Thailand     | 78                      | 9              | Ziehl-Neelsen       | 32.10%                 | NR                    |
| 29       | Sadraei J    | 2005 | India        | 200                     | 84             | Ziehl-Neelsen       | 38.00%                 | 41.00%                |
| 30       | Silva CV     | 2005 | Brazil       | 100                     | 4              | Safranin/Methylene | 38.00%                 | NR                    |
| 31       | Tadesse A    | 2005 | Ethiopia     | 70                      | 20             | Ziehl-Neelsen       | 100.00%                | NR                    |
| 32       | Tumwine JK   | 2005 | Uganda       | 91                      | 67             | IFA                 | NR                     | NR                    |
| 33       | Adhikari NA  | 2006 | Nepal        | 112                     | 6              | Ziehl-Neelsen       | NR                     | NR                    |
| 34       | Chinh S      | 2006 | Cambodia     | 80                      | 36             | Ziehl-Neelsen       | 50.00%                 | NR                    |
| 35       | Navarro-i-Martinez L | 2006 | Colombia | 103                     | 6              | PCR, Ziehl-Neelsen | NR                     | NR                    |
| 36       | Oguntibeju OO | 2006 | Lesotho      | 60                      | 6              | Ziehl-Neelsen       | 56.70%                 | NR                    |
| 37       | Sarfati C    | 2006 | Cameroon     | 154                     | 6              | Ziehl-Neelsen       | 28.60%                 | NR                    |
| 38       | de Oliveira-Silva MB | 2007 | Brazil     | 359                     | 31             | Ziehl-Neelsen       | 70.20%                 | NR                    |
| 39       | Dwivedi KK   | 2007 | India        | 75                      | 25             | Ziehl-Neelsen       | 66.70%                 | NR                    |
| 40       | Hung CC      | 2007 | Taiwan       | 332                     | 4              | PCR, Ziehl-Neelsen | NR                     | 40.10%                |
| 41       | Ramakrishnan K | 2007 | India       | 80                      | 23             | Ziehl-Neelsen       | NR                     | NR                    |
| 42       | Rossit AR    | 2007 | Brazil       | 55                      | 34             | ELISA               | 16.40%                 | NR                    |
| 43       | Stark D      | 2007 | Australia    | 628                     | 14             | Modified iron-    | hematotoxlin          | 100.00%               | NR                    |
| 44       | Taherkhani H | 2007 | Iran         | 75                      | 20             | Ziehl-Neelsen       | NR                     | NR                    |
| 45       | Vignesh R    | 2007 | India        | 245                     | 7              | Ziehl-Neelsen       | 100.00%                | NR                    |
| 46       | Bachur TP    | 2008 | Brazil       | 582                     | 47             | Ziehl-Neelsen       | NR                     | NR                    |
| 47       | Gupta S      | 2008 | India        | 113                     | 9              | Ziehl-Neelsen       | 30.10%                 | NR                    |
| 48       | Jayalakshmi J | 2008 | India       | 89                      | 11             | Ziehl-Neelsen, ELISA | 100.00%                | NR                    |
| 49       | Kaushik K    | 2008 | India        | 206                     | 27             | PCR, Ziehl-Neelsen | ELISA                 | 48.10%                | 32.50%                |
| 50       | Nuchjangreec C | 2008 | Thailand    | 46                      | 2              | PCR, Ziehl-Neelsen | 28.30%                 | NR                    |
| 51       | Racourt CP   | 2008 | Haiti        | 74                      | 45             | PCR                 | NR                     | NR                    |
| 52       | Tuli L       | 2008 | India        | 366                     | 146            | Ziehl-Neelsen       | 100.00%                | 64.50%                |

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| Paper ID | First author | Year | Country/State | Number of participants | Number infected | Diagnostic method | Patients with diarrhea | Patients with CD4<200 | Ref. |
|----------|--------------|------|---------------|------------------------|-----------------|--------------------|------------------------|----------------------|------|
| 53       | Werneck-Silva AL | 2008 | Brazil | 690 | 1 | Ziehl-Neelsen | NR | NR | [173] |
| 54       | Zaidah AR | 2008 | Malaysia | 59 | 9 | PCR, Ziehl-Neelsen | NR | NR | [182] |
| 55       | Zavvar M | 2008 | Iran | 35 | 21 | PCR, Ziehl-Neelsen | NR | NR | [184] |
| 56       | Assefa S | 2009 | Ethiopia | 214 | 43 | Ziehl-Neelsen | NR | NR | [14] |
| 57       | Daryani A | 2009 | Iran | 64 | 6 | Ziehl-Neelsen | NR | NR | [34] |
| 58       | Dillingham RA | 2009 | Haiti | 243 | 39 | Ziehl-Neelsen | NR | 100.00% | [39] |
| 59       | Gautam H | 2009 | India | 43 | 7 | ELISA | NR | 100.00% | [47] |
| 60       | Kulkarni SV | 2009 | India | 137 | 16 | Ziehl-Neelsen | NR | 47.40% | [80] |
| 61       | Kurniawan A | 2009 | Indonesia | 318 | 30 | Ziehl-Neelsen | NR | NR | [82] |
| 62       | Lule JR | 2009 | Uganda | 879 | 30 | Ziehl-Neelsen | NR | 29.90% | [90] |
| 63       | Saksirisampant W | 2009 | Thailand | 90 | 31 | PCR, Ziehl-Neelsen | NR | 78.90% | [130] |
| 64       | Uppal B | 2009 | India | 100 | 3 | ELISA | NR | 50.00% | [161] |
| 65       | Dehkordy AB | 2010 | Iran | 33 | 3 | ELISA | NR | NR | [38] |
| 66       | Getaneh A | 2010 | Ethiopia | 192 | 48 | Ziehl-Neelsen | NR | NR | [49] |
| 67       | Idris NS | 2010 | Indonesia | 22 | 1 | Ziehl-Neelsen | NR | NR | [61] |
| 68       | Kashyap B | 2010 | India | 64 | 8 | Safranin-methylene blue | NR | 48.40% | [74] |
| 69       | Tuli L | 2010 | India | 450 | 163 | Ziehl-Neelsen | NR | 100.00% | [157] |
| 70       | Akinbo FO | 2011 | Nigeria | 2000 | 80 | Ziehl-Neelsen | NR | 12.80% | [8] |
| 71       | Alemu A | 2011 | Ethiopia | 188 | 82 | Ziehl-Neelsen | NR | NR | [10] |
| 72       | Cardoso LV | 2011 | Brazil | 500 | 1 | Ziehl-Neelsen | NR | 28.60% | [25] |
| 73       | Erhabor O | 2011 | Nigeria | 105 | 3 | Ziehl-Neelsen | NR | 24.80% | [41] |
| 74       | Kucerova Z | 2011 | Russia | 46 | 19 | ELISA | NR | NR | [79] |
| 75       | Lim YA | 2011 | Malaysia | 122 | 27 | Ziehl-Neelsen | NR | NR | [88] |
| 76       | Ojurongbe O | 2011 | Nigeria | 96 | 52 | Ziehl-Neelsen | NR | NR | [112] |
| 77       | Patel SD | 2011 | India | 100 | 20 | Ziehl-Neelsen | NR | 32.00% | [118] |
| 78       | Santos RB | 2011 | Brazil | 1010 | 4 | Staining | NR | NR | [134] |
| 79       | Srisuphanunt M | 2011 | Thailand | 152 | 33 | PCR, Ziehl-Neelsen, Staining | ELISA | NR | [144] |
| 80       | Stensvold CR | 2011 | Denmark | 96 | 1 | Staining | NR | 13.50% | [146] |
| 81       | Boaitey YA | 2012 | Ghana | 500 | 70 | Ziehl-Neelsen | NR | 51.60% | [21] |
| 82       | Iqbal A | 2012 | Malaysia | 346 | 18 | PCR | NR | NR | [63] |
| 83       | Izadi M | 2012 | Iran | 47 | 7 | Ziehl-Neelsen | NR | NR | [65] |
| 84       | Jha AK | 2012 | India | 154 | 87 | Ziehl-Neelsen | NR | 35.10% | [69] |
| 85       | Kang’e the E | 2012 | Kenya | 155 | 7 | Ziehl-Neelsen | NR | NR | [72] |
| 86       | Khurana S | 2012 | India | 671 | 40 | PCR, Ziehl-Neelsen, Staining | ELISA | NR | [77] |
| 87       | Lehman LG | 2012 | Cameroon | 201 | 13 | Ziehl-Neelsen | NR | 18.40% | [86] |
| 88       | Masarat S | 2012 | India | 45 | 45 | Ziehl-Neelsen, Staining | ELISA | NR | [92] |
| 89       | Netor Velasquez J | 2012 | Argentina | 11 | 3 | PCR | NR | NR | [105] |
| 90       | Ojuromi OT | 2012 | Nigeria | 193 | 44 | Ziehl-Neelsen | NR | 34.70% | [111] |
| 91       | Pavie J | 2012 | France | 143 | 8 | Ziehl-Neelsen | NR | 59.40% | [119] |
| 92       | Roka M | 2012 | Guinea | 260 | 24 | Ziehl-Neelsen | NR | NR | [126] |
| 93       | Sharma P | 2012 | India | 970 | 44 | Ziehl-Neelsen | NR | NR | [137] |
| 94       | Tian LG | 2012 | China | 302 | 25 | Ziehl-Neelsen | NR | NR | [153] |
| 95       | Vyas N | 2012 | India | 366 | 75 | Ziehl-Neelsen | NR | 72.70% | [166] |
| 96       | Wang L | 2013 | China | 683 | 10 | PCR | NR | 44.50% | [169] |
| 97       | Adamu H | 2013 | Ethiopia | 378 | 32 | Ziehl-Neelsen | NR | 45.30% | [2] |
| 98       | Agholi M | 2013 | Iran | 356 | 34 | Ziehl-Neelsen | NR | 28.90% | [5] |
| 99       | Ahmed NH | 2013 | India | 242 | 40 | Ziehl-Neelsen | NR | NR | [6] |
| 100      | Akinbo FO | 2013 | Nigeria | 285 | 4 | PCR | NR | 37.90% | [9] |
| 101      | Assis DC | 2013 | Brazil | 59 | 6 | Ziehl-Neelsen | NR | 39.00% | [15] |
| 102      | Ayinmode AB | 2013 | Nigeria | 132 | 8 | PCR | NR | 59.80% | [16] |
| 103      | Bartelt LA | 2013 | South Africa | 193 | 146 | ELISA | NR | NR | [18] |
| 104      | Dash M | 2013 | India | 115 | 14 | Ziehl-Neelsen | NR | 36.50% | [35] |
| 105      | Gupta K | 2013 | India | 100 | 4 | Ziehl-Neelsen | NR | 19.00% | [55] |
| 106      | Janagond AB | 2013 | India | 100 | 2 | Ziehl-Neelsen | NR | 68.00% | [67] |
| 107      | Rashmi KS | 2013 | India | 90 | 15 | Ziehl-Neelsen | NR | NR | [71] |

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| Paper ID | First author | Year | Country/State | Number of participants | Number infected | Diagnostic method | Patients with diarrhea | Patients with CD4<200 | Ref.
|---------|--------------|------|---------------|-----------------------|----------------|---------------------|------------------------|-----------------------|-----------------|
| 108     | Mathur MK    | 2013 | India         | 544                   | 135            | Ziehl-Neelsen      | 73.50%                 | NR                    | [93]             |
| 109     | Mehta KD     | 2013 | India         | 100                   | 2              | Ziehl-Neelsen      | NR                     | 24.00%                | [94]             |
| 110     | Missaye A    | 2013 | Ethiopia      | 272                   | 2              | Ziehl-Neelsen      | NR                     | 10.70%                | [96]             |
| 111     | Mohanty I    | 2013 | India         | 250                   | 13             | Ziehl-Neelsen      | 80.00%                 | NR                    | [100]            |
| 112     | Teklemariam Z| 2013 | Ethiopia      | 371                   | 8              | Ziehl-Neelsen      | 20.20%                 | 27.00%                | [151]            |
| 113     | Tian LG      | 2013 | China         | 79                    | 8              | Ziehl-Neelsen      | NR                     | 100.00%               | [154]            |
| 114     | Tiwari BR    | 2013 | Nepal         | 745                   | 23             | Ziehl-Neelsen      | 33.30%                 | 43.90%                | [155]            |
| 115     | Vyas N       | 2013 | India         | 75                    | 11             | Ziehl-Neelsen      | NR                     | 42.70%                | [167]            |
| 116     | Zeynudin A   | 2013 | Ethiopia      | 91                    | 8              | Ziehl-Neelsen      | NR                     | NR                    | [185]            |
| 117     | Adamu H      | 2014 | Ethiopia      | 520                   | 140            | PCR                 | NR                     | NR                    | [1]              |
| 118     | Blanco MA    | 2014 | Guinea        | 171                   | 31             | PCR                 | NR                     | NR                    | [20]             |
| 119     | Girma M      | 2014 | Ethiopia      | 268                   | 92             | Ziehl-Neelsen      | 90.30%                 | 69.80%                | [52]             |
| 120     | Tiwari BR    | 2014 | India         | 745                   | 23             | Ziehl-Neelsen      | 33.30%                 | 43.90%                | [155]            |
| 121     | Vyas N       | 2014 | India         | 75                    | 11             | Ziehl-Neelsen      | NR                     | 42.70%                | [167]            |
| 122     | Zeynudin A   | 2013 | Ethiopia      | 91                    | 8              | Ziehl-Neelsen      | NR                     | NR                    | [185]            |
| 123     | Ahmed NH     | 2015 | India         | 142                   | 6              | Ziehl-Neelsen      | NR                     | NR                    | [7]              |
| 124     | Angal L      | 2015 | Malaysia      | 131                   | 5              | Ziehl-Neelsen      | NR                     | 18.30%                | [11]             |
| 125     | Asma I       | 2015 | Malaysia      | 346                   | 43             | Ziehl-Neelsen      | NR                     | NR                    | [13]             |
| 126     | Fregonesi BM | 2015 | Brazil        | 17                    | 4              | Ziehl-Neelsen      | NR                     | NR                    | [45]             |
| 127     | Khalil S     | 2015 | India         | 200                   | 15             | Ziehl-Neelsen      | 50.00%                 | 50.00%                | [76]             |
| 128     | Kiros H      | 2015 | Ethiopia      | 399                   | 23             | Ziehl-Neelsen      | NR                     | 16.80%                | [78]             |
| 129     | Mengist HM   | 2015 | Ethiopia      | 180                   | 7              | Ziehl-Neelsen      | NR                     | NR                    | [95]             |
| 130     | Ojuromi OT   | 2015 | Nigeria       | 90                    | 4              | PCR                 | 74.40%                 | NR                    | [110]            |
| 131     | Oyedeeji OA  | 2015 | Nigeria       | 52                    | 10             | Ziehl-Neelsen      | NR                     | NR                    | [114]            |
| 132     | Pavlinac PB  | 2015 | Kenya         | 56                    | 1              | Ziehl-Neelsen      | NR                     | NR                    | [120]            |
| 133     | Petrinová A  | 2015 | Slovak Republic| 20                 | 0              | PCR                 | NR                     | NR                    | [121]            |
| 134     | Rami H       | 2015 | Iran          | 53                    | 4              | Ziehl-Neelsen      | 100.00%                | 100.00%               | [51]             |
| 135     | Salehi Sangani G| 2016 | Iran        | 80                    | 1              | Ziehl-Neelsen      | NR                     | 100.00%               | [131]            |
| 136     | Salehi Sangani G| 2016 | Iran        | 90                    | 4              | PCR                 | 34.30%                 | NR                    | [177]            |
| 137     | Sathiraj CN  | 2017 | India         | 829                   | 19             | Modified acid-fast | 100.00%               | NR                    | [147]            |
| 138     | Swathiraj CR | 2017 | Nigeria       | 238                   | 131            | Ziehl-Neelsen      | NR                     | NR                    | [108]            |
| 139     | Thamiraj CR  | 2017 | India         | 829                   | 19             | Modified acid-fast | 100.00%               | NR                    | [147]            |
| 140     | Uysal HK     | 2017 | Turkey        | 115                   | 3              | PCR                 | 100.00%               | 28.70%                | [159]            |
| 141     | Yang Y       | 2017 | China         | 46                    | 2              | Modified acid-fast | NR                     | NR                    | [180]            |
| 142     | Yang Y       | 2017 | China         | 14                    | 3              | Modified acid-fast | NR                     | NR                    | [181]            |

Abbreviations: ELISA: Enzyme-Linked Immunosorbent Assay, IFA: Immunofluorescence Assay, PCR: Polymerase Chain Reaction, NR: not reported.
Figure 2. Forest plot diagram: The estimated pooled prevalence of Cryptosporidium infection in people with HIV infection by random-effect meta-analysis in included studies based on the PCR technique (first author, year of publication, and country). Note: The area of each square is proportional to the study’s weight in the meta-analysis, and each line represents the confidence interval around the estimate. The diamond represents the pooled estimate.
we showed that the patients with low CD4 counts had a higher prevalence rate of *Cryptosporidium* infection (*p* < 0.0001). It seems that IFN-γ is associated with T-cell memory and is a critical regulator of both innate and adaptive immune responses against *Cryptosporidium* infection. Also, the findings of immunological research suggest that *Cryptosporidium* induced an inflammatory response in intestinal epithelial cells. Accordingly, the higher expression of inflammatory and pro-inflammatory cytokines, such as CXCL-10 and substance P is present in AIDS patients (compared to AIDS patients without cryptosporidiosis or negative controls) [116]. The opportunistic parasites *Cryptosporidium* spp. are not only associated with the immune state in HIV-infected patients, but are also more evident with antiretroviral therapy. Utilization of chemoprophylaxis could increase the immunity of HIV-positive individuals and reduce the infection. Our findings suggested that in HIV-infected patients, especially with low CD4 counts, ART should be prescribed.

Substantial heterogeneity was observed between the studies included in this meta-analysis. In addition to using the random-effects model, which incorporates some of this heterogeneity, we investigated possible causes of heterogeneity and compared the estimated prevalence in different subgroups and settings [37]. The diagnostic method that was used to detect

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**Figure 3.** Forest plot diagram: The estimated pooled prevalence of *Cryptosporidium* infection in people with HIV infection by random-effect meta-analysis in included studies based on serological methods (first author, year of publication, and country). Note: The area of each square is proportional to the study’s weight in the meta-analysis, and each line represents the confidence interval around the estimate. The diamond represents the pooled estimate.

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Silva CV, 2003, Brazil 0.135 (0.056, 0.258)
Marques FR, 2005, Brazil 0.085 (0.037, 0.161)
Houpt ER, 2005, Tanzania 0.173 (0.112, 0.250)
Tumwine JK, 2005, Uganda 0.736 (0.633, 0.823)
Rosit AR, 2007, Brazil 0.618 (0.477, 0.746)
Kaushik K, 2008, India 0.198 (0.138, 0.250)
Jayalakshmi J, 2008, India 0.112 (0.055, 0.197)
Uppal B, 2009, India 0.030 (0.006, 0.085)
Gautam H, 2009, India 0.163 (0.068, 0.307)
Dehkordy AB, 2010, Iran 0.091 (0.019, 0.243)
Kucerova Z, 2011, Russia 0.413 (0.270, 0.568)
Omoruyi B, 2011, South Africa 0.000 (0.900, 1.000)
Srisuphanunt M, 2011, Thailand 0.270 (0.201, 0.348)
Mesarat S, 2012, India 0.000 (0.921, 1.000)
Khurana S, 2012, India 0.048 (0.033, 0.067)
Bartelt LA, 2013, South Africa 0.756 (0.690, 0.815)
Omoruyi BE, 2014, Africa 0.743 (0.567, 0.875)
Uppal B, 2014, India 0.672 (0.537, 0.790)
Zhang L, 2015, China 0.137 (0.091, 0.194)
Kanyarakal V, 2016, India 0.025 (0.008, 0.057)
combined 0.355 (0.213, 0.512)
Cryptosporidium infection significantly influenced the estimated prevalence. The included studies had utilized three main categories of diagnostic methods. PCR is considered the gold standard in diagnosing Cryptosporidium infection with an excellent sensitivity of 97% and specificity of 100%, but is not commonly used due to its high cost and high expertise requirement, especially in low-income countries [28]. The estimated pooled prevalence using PCR was 16.5%, which could be considered as the "real" prevalence. Conventional microscopy, most commonly using Ziehl-Neelsen staining, is an inexpensive and widely available method but has a low sensitivity of 75% [27]. The estimated pooled prevalence using staining methods was 11.9%, which was the lowest estimate among used diagnostic methods. Enzyme Immunoassays (EIA), based on detection of Cryptosporidium antigens, cost more than the staining methods and have a moderate to high diagnostic accuracy, with a sensitivity of 75%–93%. However, confirmatory testing has been suggested when using EIA, since some false-positive reactions have been confirmed [27, 28, 172]. The pooled prevalence using antigen detection methods was the highest among diagnostic methods with an estimate of 35.5%. In addition to false-positive reactions, we propose that the higher prevalence in studies that utilized EIA methods could be due to possible continued shedding of Cryptosporidium antigens in the stools, even after the resolution of infection, although this effect has not been studied.

The geographical distribution was another confounding factor. The estimated prevalence within countries was in a range of 1% in Denmark to 57% in South Africa. Among the countries with more than ten included studies, India (14.1%), Iran (11.1%) and Nigeria (10.6%) had the highest prevalence. The economic status of different countries could be the most probable explanation for these findings. The prevalence in high-income countries, with an estimate of 4.1%, was significantly lower than in middle and low-income countries, but there was no statistically significant difference between the estimated prevalence in the middle-income and low-income countries. Additionally, the source of drinking water can contribute to the different prevalence observed within different countries. A meta-analysis showed that drinking unsafe water significantly increases the risk of Cryptosporidium infection [53]. However, we were unable to evaluate its effect on prevalence since very
Figure 5. Pooled prevalence of Cryptosporidium in HIV-positive patients in different countries (source of image: https://commons.wikimedia.org/wiki/File:BlankMap-World.svg).

Table 2. Pooled prevalence of Cryptosporidium in HIV-positive patients and subgroup analyses.

| Group                      | Number of studies | Pooled prevalence (CI 95%) | Heterogeneity | p-value |
|----------------------------|-------------------|----------------------------|---------------|---------|
| Diagnostic method          |                   |                            |               | p < 0.05|
| Staining                  | 140               | 10.0% (8.4%–11.8%)         | <0.001        | 96.00   |
| Antigen detection          | 19                | 26.3% (15.0%–42.0%)        | <0.001        | 96.90   |
| Molecular                  | 28                | 13.5% (8.9%–19.8%)         | <0.001        | 95.60   |
| Country*                   |                   |                            |               | p < 0.05|
| Brazil                    | 12                | 5.4% (2.5%–11.6%)          | <0.001        | 93.90   |
| China                     | 6                 | 7.2% (3.5%–14.3%)          | <0.001        | 87.50   |
| Ethiopia                  | 18                | 9.8% (6.5%–14.7%)          | <0.001        | 95.70   |
| India                     | 41                | 14.1% (10.5%–18.7%)        | <0.001        | 95.90   |
| Iran                      | 10                | 11.1% (6.0%–19.5%)         | <0.001        | 89.40   |
| Malaysia                  | 7                 | 9.1% (5.0%–15.8%)          | <0.001        | 86.60   |
| Nigeria                   | 11                | 10.6% (3.9%–25.6%)         | <0.001        | 98.30   |
| Thailand                  | 8                 | 11.0% (6.2%–18.7%)         | <0.001        | 85.40   |
| Region                    |                   |                            |               | p = 0.46|
| African Region            | 53                | 11.9% (8.8%–16.0%)         | <0.001        | 97.00   |
| Eastern Mediterranean Region| 10                | 11.1% (6.0%–19.5%)         | <0.001        | 89.40   |
| European Region           | 5                 | 5.4% (1.0%–23.7%)          | <0.001        | 92.00   |
| Region of the Americas    | 23                | 9.8% (6.4%–14.8%)          | <0.001        | 97.30   |
| South-East Asia Region    | 53                | 12.7% (9.7%–16.4%)         | <0.001        | 95.50   |
| Western Pacific Region    | 17                | 7.7% (4.7%–12.3%)          | <0.001        | 92.60   |
| Income Level              |                   |                            |               | p = 0.43|
| High income               | 8                 | 4.1% (2.4%–6.9%)           | <0.001        | 77.80   |
| Upper-middle income       | 52                | 10.4% (8.0%–13.5%)         | <0.001        | 94.10   |
| Lower-middle income       | 68                | 13.1% (10.2%–16.6%)        | <0.001        | 96.30   |
| Low income                | 33                | 10.9% (7.6%–15.2%)         | <0.001        | 96.30   |
| Number of Participants    |                   |                            |               | p < 0.05|
| <100                      | 66                | 15.4% (11.8%–19.8%)        | <0.001        | 91.00   |
| >100                      | 95                | 8.9% (7.2%–11.0%)          | <0.001        | 97.30   |

* Only countries with more than 5 included studies are shown.
few studies reported the sources of drinking water. Our study showed that the pooled prevalence across WHO Global Burden of Disease regions was not significantly different.

The association of Cryptosporidium prevalence and the proportion of symptomatic HIV patients has been investigated. No statistically significant difference was observed between the prevalence in studies with a high proportion of symptomatic patients and studies with a low proportion of symptomatic patients, although the meta-regression showed a correlation between prevalence and the proportion of symptomatic patients. Another significant confounding variable was the number of participants in the included studies. Studies with a lower number of participants reported higher prevalence rates. This could be due to the fact that lower sample sizes are associated with higher sampling error [133].

The studies also differed in the period when they were conducted, but meta-regression showed that the year of publication did not correlate to estimated prevalence. A meta-analysis suggested seasonality in the prevalence of Cryptosporidium, and showed that precipitation and temperature are strongly associated with the rate of infection [66]. However, it was not possible to investigate the impact of seasons and different climates on the prevalence in the present meta-analysis, due to the limited data reported. Nonetheless, the heterogeneity after considering these confounding variables was still high. Other unknown and uninvestigated differences in study design and population might exist, but it is not uncommon for meta-analyses to have high heterogeneity. In addition to high heterogeneity, our study was also limited by the publication bias. This occurs when the results of studies influence the decision of the author or publisher. Therefore, we recommend developing a database of HIV patients infected with Cryptosporidium to estimate the overall prevalence of cryptosporidiosis and the geographical and time distribution of infection more accurately.

**Conclusion**

The prolonged and severe diarrhea caused by Cryptosporidium is associated with significant morbidity and mortality, especially in the HIV-infected population. This highlights the importance of preventive measures such as drinking safe water, using community-based or household water treatment systems, and education on hand hygiene after using toilets and before preparing food. Additionally, clinicians should consider early symptoms of cryptosporidiosis, such as diarrhea, in HIV patients, with the aim of initiating treatment early in the disease course. Also, patients with a CD4 count below 200 should receive prophylactic antiparasite treatment. If implemented correctly, these measures could lead to decreased morbidity, mortality, and transmission.
Conflict of interest

Authors declare there is no conflict of interest.

Funding

This study was supported by the Research Center for Evidence Based Medicine (RCEBM), Tabriz University of Medical Sciences, Tabriz, Iran.

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Cite this article as: Ahmadpour E, Safarpour H, Xiao L, Zarean M, Hatami-Nahavandi K, Barac A, Picot S, Rahimi MT, Rubino S, Mahami-Oskouei M, Spotin A, Nami S & Baghi HB. 2020. Cryptosporidiosis in HIV-positive patients and related risk factors: A systematic review and meta-analysis. Parasite 27, 27.