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Balantidiasis in humans: A systematic review and meta-analysis

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ABSTRACT

Balantioides coli is a protozoan that infects different hosts species, including humans, with zoonotic transmission. The parasite, which lives in the large intestine and in other organs, can lead to serious infections that may culminate in death. Information about human balantidiasis is generally still very scanty. In view of the above, the purpose of this study was to analyze the epidemiological, clinical and laboratory characteristics of human balantidiasis based on a systematic review and meta-analysis. The scientific articles were retrieved from various databases and were subjected to descriptive analyses, chi-squared tests, and summarized on a forest plot and the heterogeneity index (I^2). A total of 103 articles were eligible and included in this review. Out of these 103 articles, 75 were clinical case reports and 28 were epidemiological studies, indicating a frequency of 997 (3.98%) people potentially infected with *B. coli*. The publication dates of the analyzed articles ranged from 1910 to 2020, but the majority (68.9%) were published between 1998 and 2020. A considerable number of these articles were published in South America and Asia, mostly in Brazil and India, respectively. However, in Africa, Ethiopia, was observed the higher number of infected people (47.5%). A significant association ($p < 0.05$) was identified between proximity to pigs and positivity for *B. coli*, since more than 16% infected people were in proximity with pigs and/or their excreta. Infection by the protozoan was classified mainly as intestinal, and the predominant symptom was dysentery. Extraintestinal infections were found in 27 individuals, with colonization of the genitourinary tract frequently highlighted. Direct examination (17.2%), followed by an association of direct examination and sedimentation (45.7%), were the most commonly performed parasitological techniques, and the most frequently diagnosed form was trophozoites, corresponding to 22.5% of cases. The most common treatment for parasitized individuals (11.8%) was an association of tetracycline drugs with nitroimidazole derivatives. The articles retrieved, mainly epidemiological ones, used in meta-analysis showed high heterogeneity ($I^2 > 50\%$, $p < 0.05$), impairing the retrieval and comparison of results. Some articles were found to provide incomplete information, making it difficult to retrieve and analyze variables. However, this review enabled us to compile and restate factors that appear to be associated with cases of human balantidiasis.

1. Introduction

Balantidiasis is a parasitic disease caused by the protozoan *Balantioides coli*, formerly known as *Balantidium coli*, a protozoan that infects animals including pig, non-human primates and humans, and has a zoonotic transmission potential (Chistyakova et al., 2014; Ahmed et al., 2020). Infection in humans by this parasite is known as balantidiasis, balantidial dysentery, or ciliary dysentery (Barbosa et al., 2018a). The parasite's habitat is the large intestine, mainly the cecum and colon. However, atypical extraintestinal colonization may also occur (Schuster and Ramirez-Ávila, 2008).

Basically, the parasite has two forms, the cyst and the ciliated trophozoites. The cyst is the resistant form in the environment, and therefore the infectious form. The ciliated trophozoite is the active form

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of the parasite, which multiplies in the intestinal lumen, tissue and organs of the host, and therefore considered the pathogenic form (Zaman, 1978; Barbosa et al., 2018b). ***Balantioides coli***, which is considered the only parasitic ciliated protozoan in humans, is transmitted mainly through the ingestion of cysts that contaminate water and food, particularly fruits and vegetables (Solaymani-Mohammadi and Petri, 2006; Barbosa et al., 2018a).

In humans, infections by this protozoan may occur asymptomatically or symptomatically. In the latter case, infections may present in chronic form, characterized by episodes of intermittent diarrhea, without the presence of blood, with colic and abdominal pain, or in acute form, characterized by dysentery, i.e liquefied stools containing mucus and blood that may lead to fulminant clinical conditions (Zaman, 1978; Vásquez and Vidal, 1999). In extraintestinal infections have also been reported including peritonitis, urogenital tract and pulmonary inflammations (Wenger, 1967; Dorfman et al., 1984; Kaur and Gupta, 2016).

Balantioides coli is considered a parasite of worldwide distribution, since infection by this protozoan has already been reported in several countries on different continents. However, the epidemiological rates of infection caused by this protozoan are still very scanty, and balantidiasis is a highly neglected disease (Schuster and Ramirez-Ávila, 2008; Solaymani-Mohammadi and Petri, 2006). The scientific literature still offers very little information and studies about this protozoan, with publications generally fragmented, especially when it comes to human infections reported in articles about clinical cases. This situation highlights the need for a systematic review to gather and analyze the information. In view of the above, this study focused on a pioneering analysis of epidemiological, clinical and laboratory information about cases of human balantidiasis, based on a systematic review and meta-analysis of scientific articles retrieved from different databases.

2. Material and methods

2.1. Retrieval of articles from databases

A systematic search of scientific articles was carried out between between July 2019 to July 2020 in an indexed database on the theme of balantidiasis in humans. Search descriptors in Portuguese, Spanish and English were used, as well as the scientific names in Latin already assigned to the etiological agent, as described in Chart 1. The following databases were searched: SciELO (Scientific Electronic Library Online), PubMed, Medline, LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Organization, ISI Web of Science and Google Scholar.

Chart 1
Descriptors used to search for scientific articles on balantidiasis in humans in the scientific databases.

Scientific name of the parasite		*Balantidium coli* *Balantidium* *Balantioides coli* *Balantioides* *Neobalantidium coli* *Neobalantidium*	
	Portuguese	**Spanish**	**English**
Name of parasitosis and / or infection	Balantidiose Balantidíase disenteria balantidiana infecção balantidiana *Balantidium* infecção	Balantidiose Balantidíase disenteria balantidiana Infección balantidiana *Balantidium* Infección	Balantidiosis Balantidiasis cyliari dysentery *Balantidium* infection *Balantidium* infections
Intestinal infection	*Balantidium* diarreia *Balantidium* disenteria *Balantidium* colite *Balantidium* tiflite	*Balantidium* diarrea *Balantidium* disentería *Balantidium* colitis *Balantidium* tiflito	*Balantidium* diarrhea *Balantidium* disenteric *Balantidium* colitis *Balantidium* typhitis
Extraintestinal infection	*Balantidium* extraintestinal	*Balantidium* extraintestinal	*Balantidium* extraintestinal
Genitourinary tract infection	*Balantidium* urina *Balantidium* hematuria *Balantidium* urinaria	*Balantidium* orine *Balantidium* hematuria *Balantidium* urinaria	*Balantidium* urine *Balantidium* hematuria *Balantidium* urinary
Respiratory tract infection	*Balantidium* pulmão *Balantidium* pneumonia *Balantidium* pulmonar	*Balantidium* pulmón *Balantidium* neumonía *Balantidium* pulmonar	*Balantidium* lung *Balantidium* pneumonia *Balantidium* pulmonary
Hepatic infection	*Balantidium* fígado *Balantidium* abscesso	*Balantidium* hígado *Balantidium* absceso	*Balantidium* liver *Balantidium* abscess
Infection in the peritoneum and appendix	*Balantidium* peritonite *Balantidium* peritônio *Balantidium* apendicite *Balantidium* apêndice	*Balantidium* peritonitis *Balantidium* peritoneo *Balantidium* apendicitis *Balantidium* apéndice	*Balantidium* peritonitis *Balantidium* peritoneum *Balantidium* appendicitis *Balantidium* appendix
Vertebrae and bones infection	*Balantidium* vertebra *Balantidium* osteomielite *Balantidium* osso	*Balantidium* vertebral *Balantidium* osteomielitis *Balantidium* hueso	*Balantidium* vertebral *Balantidium* osteomyelitis *Balantidium* bone

2.2. Identification and suitability of the articles

The retrieved articles on human balantidiasis were identified based on their titles and technical information of the publication, such as name of the author, journal, volume and number. This enabled us to remove repetitions of articles, i.e., articles retrieved from more than one database. After this procedure, the articles were selected to determine their eligibility, with screening performed by reading their titles, abstracts and results, and checking them against the inclusion and exclusion criteria.

Inclusion criteria for this systematic review were:

- Full texts of scientific articles available online or in libraries for consultation at the research site;
- Articles on clinical cases of balantidiasis in humans;
- Epidemiological research articles, including prospective and retrospective studies about *B. coli* infection in humans or intestinal parasites;
- Articles reporting *B. coli* infection in humans, regardless of publication dates;
- Articles retrieved in Portuguese, Spanish, English and French versions.

Exclusion criteria for the study were:

- Studies of human balantidiasis published solely in the form of monograph/dissertation/thesis or abstracts at Conferences;
- Articles on molecular epidemiology and experimental studies, including *in vitro* and *in vivo* inoculations;
- Review articles on parasitic infections and book chapters;
- Epidemiological articles aimed at detecting *B. coli* in humans, but that did not diagnose the parasite;
- Articles that discussed only biological samples from other host species and environmental samples.

2.3. Inclusion of articles and tabulation of data

The eligible articles included in this study were read thoroughly to retrieve information, which was stored on Microsoft Excel® spreadsheets. The following information was sought for in the articles:

- *Year:* Year of publication or accept of the article.
- *Authors:* Name(s) of the author(s).
- *Country and Continent:* Information was retrieved about the country of origin of the patient and/or the person included in the study. However, when such information was not available in the article, information was sought about the hospital that provided treatment, the institution that processed the biological sample, and lastly the country of origin of the institution to which the authors were affiliated. This, in turn, enabled identification of the continent.
- *Study:* The study design was classified as Clinical case report (CR) or Epidemiological (E) study.
- *Age/Sample group:* The age of the individual participating in the study was primarily retrieved in numbers. However, it was not always presented this way, and was therefore determined based on a previous classification of the authors of the articles involving children, teenagers, adults, or the elderly. From the ages retrieved in numbers, it was also possible to classify the individuals participating in the studies as children between zero and 12 years old, teenagers between 13 and 19 years old, adults from 20 to 59 years old, and as elderly participants 60 years or older. Sample group: the number of people testing positive in each age group, when provided, was also retrieved.
- *Sample number and Positivity:* Information about the number of people included in the study was listed in the variable of sample number, while information about the total number of positive people, i.e., those infected by the parasite, was catalogued in the variable of Positivity for *B. coli* (P).
- *Comorbidities/Concomitant infections:* This variable consisted of information about other physiological changes, diseases and/or infective agents in the participants of the study;
- *Use of alcohol:* The habit of frequent consumption of alcoholic drinks by the individuals included in the study.
- *Proximity to pigs and/or their excreta:* When the individuals included in the study handled or lived in proximity to pigs and/or their excreta.
- *Intestinal and/or extraintestinal balantidiasis:* When the parasite was detected in the gastrointestinal tract, the infection was classified as intestinal balantidiasis. When the parasite was detected in other organs, the infection was considered extraintestinal and the organ or tissue in which it was detected was described.
- *Clinical symptoms:* Symptoms reported by infected individuals.
- *Fecal samples collected/with or without preservative/number of samples:* Information about the coproparasitological diagnosis based on a stool sample from the patient was included on the spreadsheet, as was information about the stool collection procedure, the use or not of chemical preservatives, and the number of stool samples collected.
- *Laboratory technique performed:* This variable included the name of the coproparasitological technique used and/or other laboratory techniques that were important for the diagnosis of the parasitic infection, especially in cases of extraintestinal infection.
- *Detected form:* Information was also retrieved about the forms of the diagnosed parasite, i.e., trophozoites and/or cysts.
- *Treatment performed:* The procedure employed to eliminate the parasitic infection, through medication or another method.
- *Repetition of diagnosis after treatment:* When the article reported that laboratory tests were performed after conclusion of the individual's parasitological treatment.
- *Clinical outcome:* Information provided in the articles about the final outcome of the diagnosis and/or treatment of the individual included in the study. The individual was classified as recovered, when information was provided about his clinical and/or parasitological cure, or as dead.

Whenever any article did not present pertinent information clearly, it was classified as "*N*", i.e., not reported. All the articles included in this systematic review were accounted for, and were also classified according to the type of article, i.e., epidemiological – retrospective or prospective studies of frequency, or medical case reports. The categories retrieved for each variable were described in absolute and relative values (%). However, it should be noted that more than one category could be described per article. In that case, the article had to be listed more than once, so the sum of the values found for this variable may have exceeded the total number of articles retrieved from the databases.

In addition to counts per article, category-related information was described per person diagnosed with *B. coli*. This count per individual was presented in absolute and relative values (%), and because it is a count per individual, the sum of the categories of each variable is compatible with the total sum of positive people obtained by associating all the articles.

2.4. Presentation of results and statistical analysis

Information concerning the systematic review was descriptively presented in tables, based on qualitative and quantitative data. The countries where publications about human balantidiasis were retrieved were marked in gray color, with those with the highest number of people potentially infected by the protozoan being marked in different color gradient of lilac on a world map, using ArcGis® v. 10.5 software. When articles contained complete information about their sampling distributed in different categories, these were compared using the Chi-square test at a 5% level of significance, which was calculated using

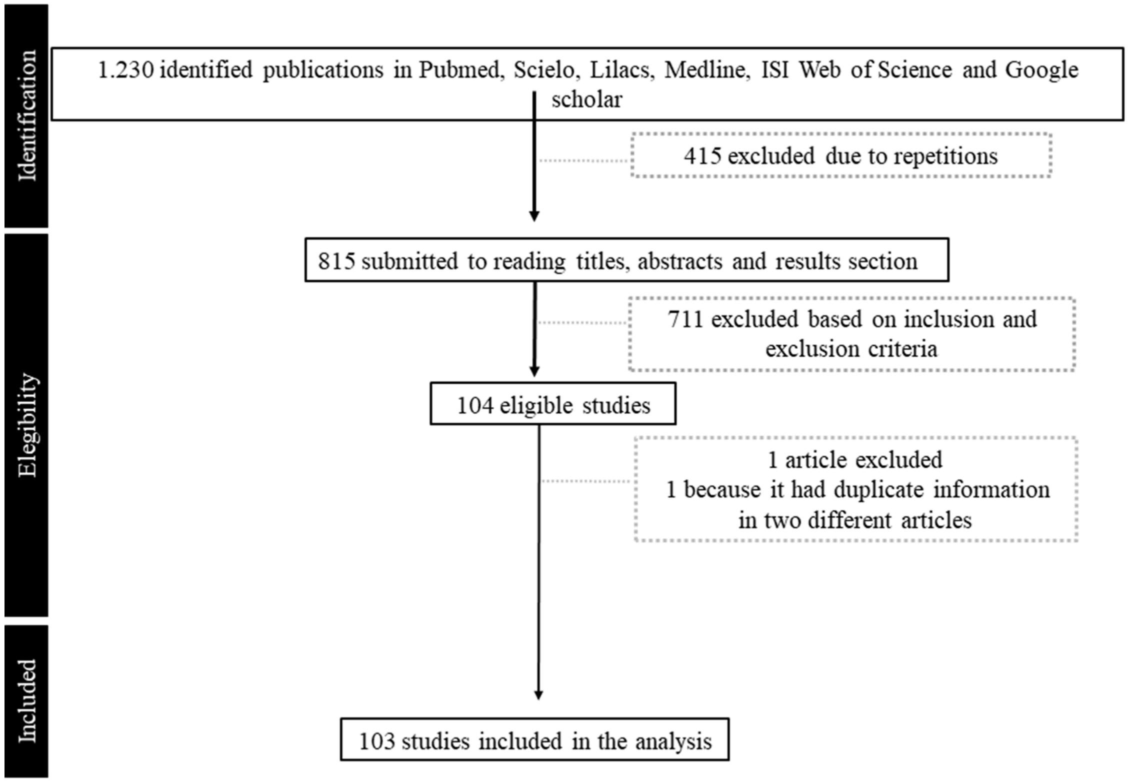

Fig. 1. Flowchart of the selection of articles on human balantidiasis analyzed in the systematic review and meta-analysis.

Table 1
Number of scientific articles and different types of information retrieved about people potentially infected with *Balantioides coli*.

Information	Articles analyzed (n = 103)		Number of case reports (n = 75)		Number of epidemiological studies (n = 28)		Number of people infected with *Balantioides coli* (n = 997)		p value
Year publication/accept intervals	n	%	n	%	n	%	n	%	
1910–1931	5	4.9	5	6.7	0	0	8	0.8	
1932–1953	7	6.8	7	9.3	0	0	102	10.2	
1954–1975	7	6.8	7	9.3	0	0	120	12	$P < 0.0001$
1976–1997	13	12.6	9	12	4	14.3	21	2.1	
1998–2020	71	68.9	47	62.7	24	85.7	746	74.8	
Continent									
South America	30	29.1	19	25.3	11	39.3	78	7.8	
Central America	5	4.9	4	5.3	1	3.6	18	1.8	
North America	16	15.5	15	20	1	3.6	55	5.5	
Africa	7	6.8	1	1.3	6	21.4	474	47.5	$P < 0.0001$
Asia	31	30.1	24	32	7	25	248	24.9	
Oceania	3	2.9	3	4	0	0	112	11.2	
Europe	10	9.7	8	10.7	2	7.1	11	1.1	
Europe and Asia	1	1	1	1.3	0	0	1	0.1	
Proximity to pigs									
Yes	26	25.2	22	29.3	4	14.3	165	16.5	
No	21	20.4	20	26.7	1	3.6	107	10.7	$P < 0.0001$
Not reported	57	55.3	33	44	24	85.7	725	72.7	

*$p < 0.05$

GraphPad Prism® v. 6. In addition, retrievable information (period and continent of publication) from epidemiological articles was subjected to meta-analysis through a random effects model for the proportion of human balantidiasis cases, resulting in the creation of a forest plot containing the estimate and a 95% confidence interval. The heterogeneity index (I^2) was used to assess the consistency of the information described in the articles at a 5% significance level. An I^2 higher than 50% indicated substantial heterogeneity, and above 75% indicated considerable heterogeneity. The entire meta-analysis was performed using the statistical computing software R version 4.0.3.

3. Results

Through the searches with descriptors, 1230 articles were retrieved from the databases listed earlier herein. After reading the titles and technical information about each publication, such as the name of the author, the magazine, volume and number, 415 repeated articles were removed from the analysis, which left 815 studies. The next step consisted of analyzing the articles for eligibility, which involved reading their titles, abstracts and results, that were checked in relation to the inclusion and exclusion criteria. This analysis resulted in the exclusion of 711 studies that did not meet the criteria, leaving 104 scientific articles that were considered eligible. All of these articles were read in their

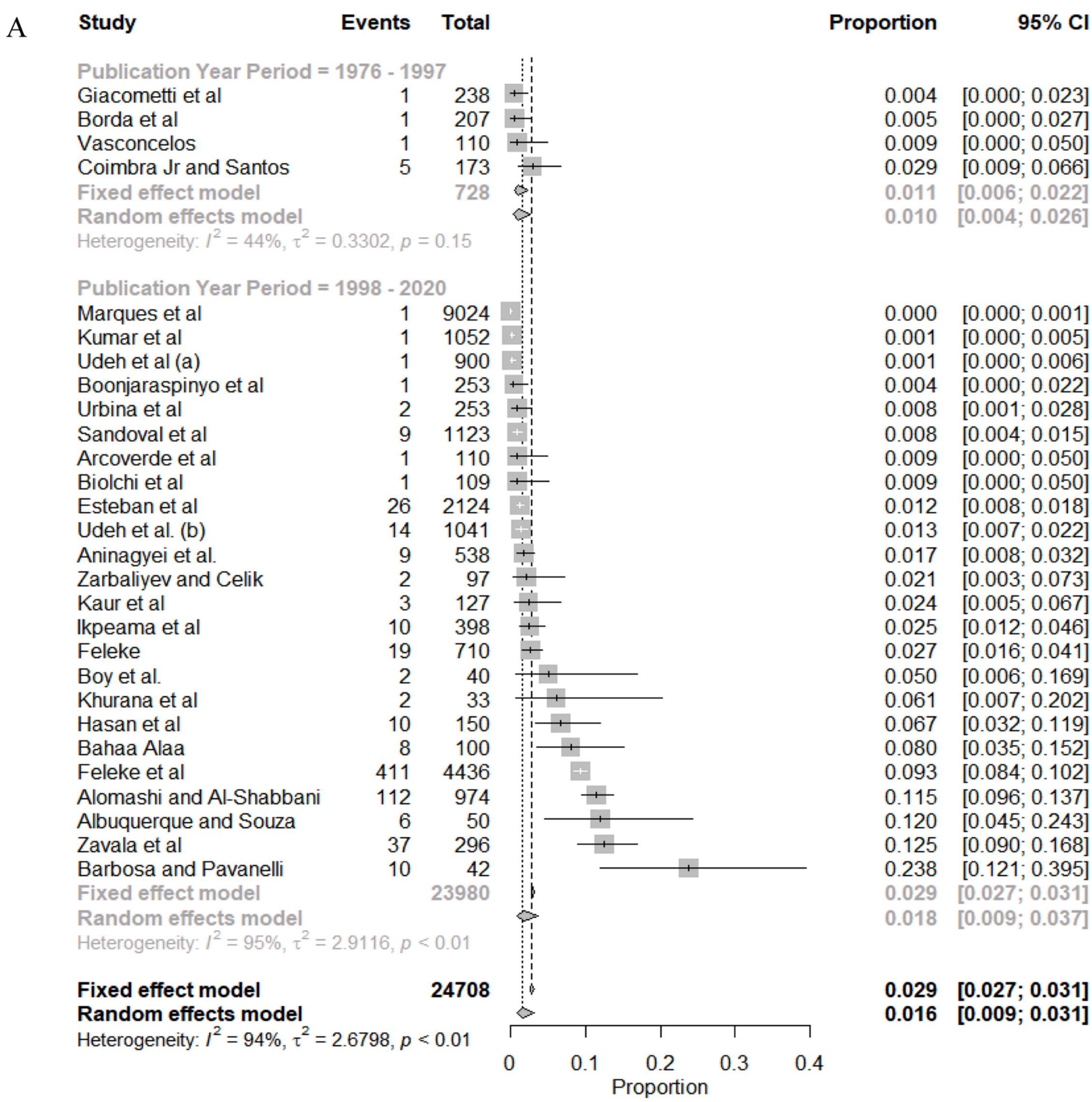

Fig. 2. Forest plot of the epidemiological studies retrieved on human balantidiasis analyzed according to the subgroups: (A) Year of publication, and (B) Continent of publication.

entirety, leading to the discovery that two scientific articles with different titles contained the same information and were authored by the same group of researchers, but were published in different journals. The article that contained more complete information and directly addressed human balantidiasis was included in the study, while the other one was discarded, leaving 103 publications for this systematic analysis (Fig. 1). Of these, 75 were clinical case reports while 28 were epidemiological studies, but only the latter served for our meta-analysis (Table 1). The joint analysis of all these articles, both clinical case reports and epidemiological studies, represented a total of 24,999 human participants.

Although 24,999 participants were included in this review, only 997 (3.98%) were considered potentially infected with the protozoan *B. coli*. In general, the meta-analysis of the 28 selected epidemiological articles confirmed their high degree of heterogeneity with respect to the proportion of the human balantidiasis ($I^2 = 94\%$, $p < 0.01$). As a final result of the random effects model, which is the most suitable one in the case of high heterogeneity, the combined estimate for the proportion of cases of balantidiasis would be 0.016 (95% CI: [0.009, 0.031]).

The stratification of eligible articles into 22 or 23-years publication intervals revealed that 68.9% of them belonged to the most recent time interval (1998–2020). There was a decline in the number of scientific articles on human balantidiasis that were retrieved as publication dates went back in time (Table 1). The highest positivity rate for parasitic infections among humans was found between 1998 and 2020 (74.8%), followed by the interval of 1954–1975 (12%) and of 1932–1953 (10.2%) (Table 1). Despite these differences, an evaluation of the effect of the periods of publication of epidemiological articles in the model indicated that the residual heterogeneity remained high (I^2: 94%, $p<0.01$) with a greater proportion of the human balantidiasis event occurring in the most recent year interval (Fig. 2A).

As for the continents of origin of the publications, most of the eligible scientific articles that were retrieved were published in Asia (30.1) and South American countries (29.1%), followed by North America (15.5%). However, in the 103 selected articles, the largest number of individuals with balantidiasis was detected in Africa followed by Asia. A comparison of the proportion of positive individuals per continent revealed statistically significant differences ($p<0.05$, Table 1). The meta-analysis of epidemiological studies indicated that heterogeneity was higher among articles (I^2=94%, $p<0.01$), with a greater proportion of the human balantidiasis event occurring again in South America and Asia (Fig. 2B).

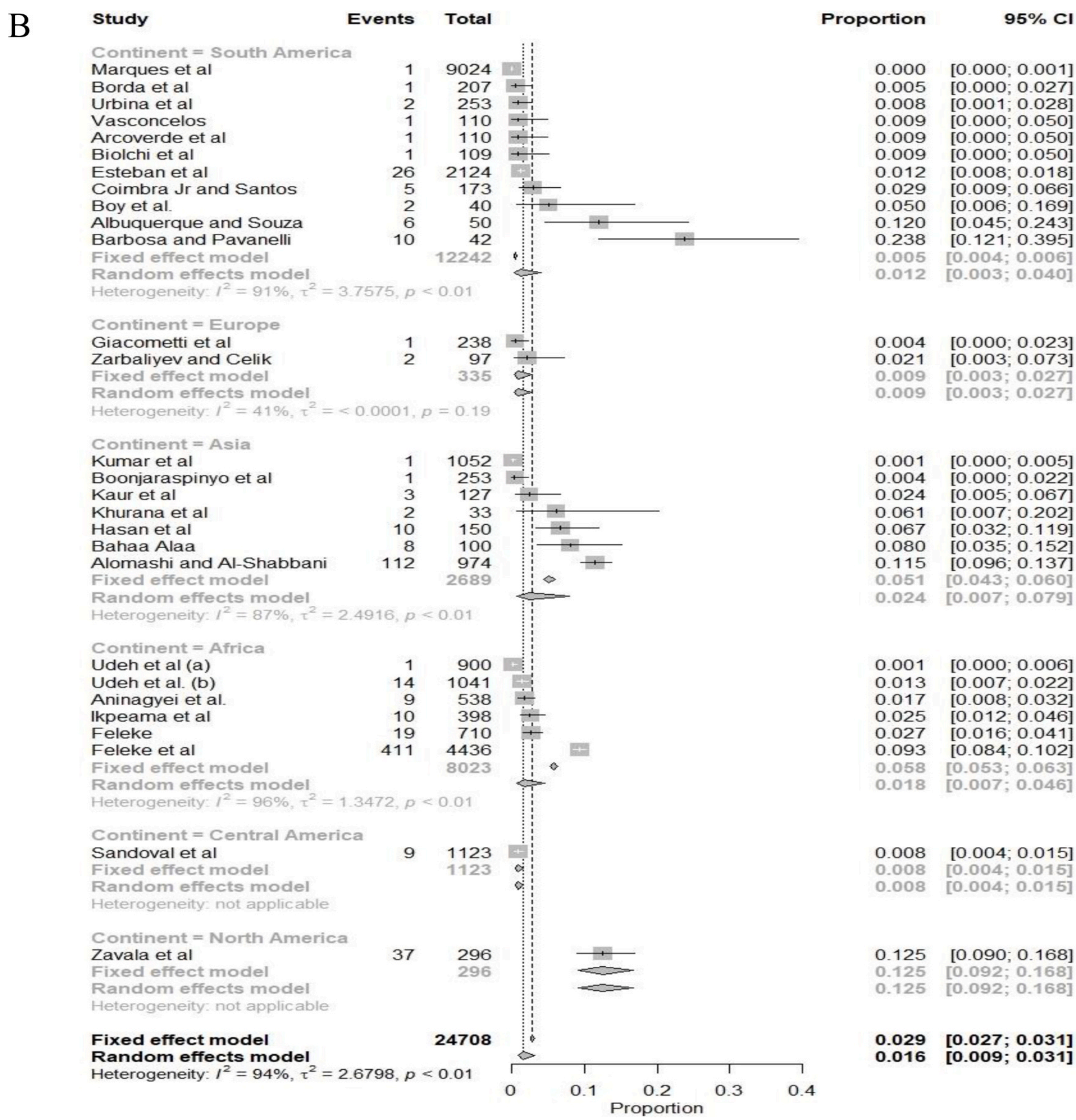

Fig. 2. (*continued*).

The Fig. 3 depicts the countries where articles were retrieved that reported infections potentially determined by *B. coli* and those with the highest frequencies of parasitosis plotted on a lilac and gray color gradient. With regard to countries, this Fig. indicates that the largest number of infected people among the publications retrieved and published until the year 2020 occurred in Ethiopia, Iraq, Truk Island, Iran, Mexico, Brazil, Bolivia, India, the United States and Bangladesh.

The demographic data of the individuals included in the studies indicated that the sample population of most of the studies were adults. However, in the case of the majority of individuals potentially positive for *B. coli*, this information was not provided in the article (62.1%), this case was found in most of the epidemiological studies (57.1%). Among the articles that reported the age of individuals, higher *B. coli* positivity rates were reported among children than among adults. Around 49.5% of the articles reported that the individuals potentially infected by *B. coli* had some comorbidity and/or concomitant infections caused by other biological agents. The association of these with infection by ciliated protozoa such as *B. coli* represented 21.5% of the positive individuals included in this review. Only six articles, corresponding to six infected individuals, presented evidence of alcohol abuse (Table 2).

Information about permanent and/or occasional proximity to pigs and their excreta was reported in 25.2% of scientific articles, representing more than 16.5% of the individuals considered positive for *B. coli*. In addition, this variable of proximity to pigs showed a statistically significant difference ($p<0.05$) in a comparison of the different groups of individuals included in the studies and potentially positive for *B. coli*, classified according to the information provided in the article (Table 1).

The location of the ciliate in the large intestine, its habitat of choice, proportionally represented more than 95% of the infected individuals, while exclusively extraintestinal infections were observed in 27 individuals. Extraintestinal infection sites were described mostly in clinical case reports, in which the parasite potentially colonized mainly the genitourinary tract, followed by the lungs, peritoneum, eyeballs, liver, gallbladder and vertebra. About 21.4% of the studies did not report the presence or absence of symptoms in parasitized individuals. Among those that provided this information, symptomatic cases corresponded to 79.6% of the article retrieved. The most frequently reported clinical manifestations of the intestinal form of infection were dysentery (12.8%) and tenesmus (9.6%), while extraintestinal infections involved dysuria, dyspnea, hemoptysis, pain in the right hypochondrium, abdominal distension, red eyes, photophobia and foreign body sensation

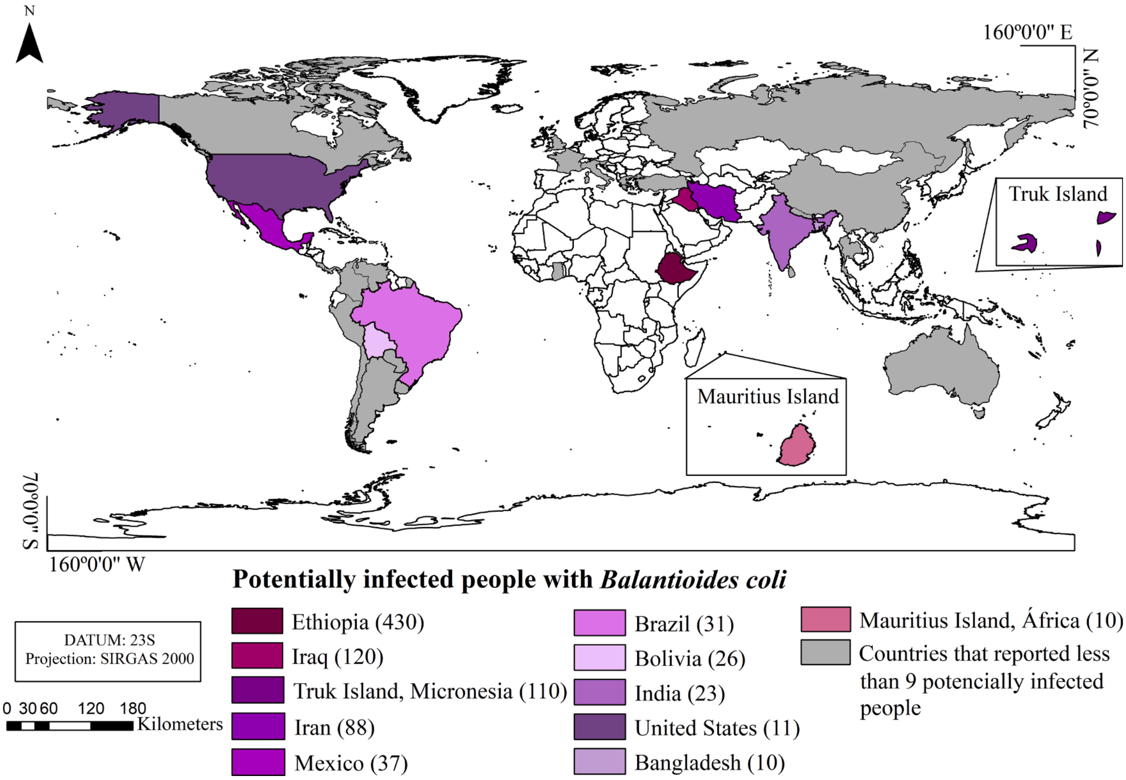

Fig. 3. Distribution of scientific articles on human balantidiasis retrieved for this study.

in the eye (Table 2).

Diagnostic information retrieved for this analysis revealed that more than 80% of the articles contained information about the collection of stool samples for coproparasitological diagnosis; in other words, laboratory techniques were applied to over 90% of individuals potentially infected with *B. coli.* Although 49.5% of these studies did not report the use of chemical preservatives to preserve stool samples, 25.2% of the articles, most of them describing clinical case reports, clearly stated that stool samples were collected without chemical preservatives. As for diagnostics, most of the studies included in this review did not describe the amount of stool sample analyzed per patient (47.6%) and not even the coproparasitological technique employed (36.9%). In general, information on coproparasitological laboratory techniques most commonly retrieved from the articles was direct examination (17.5%), followed by a combination of direct examination and sedimentation (6.8%). Proportionally, direct examination accounted for the diagnosis of balantidiasis in 17.2% infected individuals, while the combination of techniques accounted for the diagnosis of 45.7% individuals (Table 2).

The form most frequently identified in the stool of infected people was trophozoites, which were detected in 22.5% (Table 3). This evolutionary form was also the most frequently detected in other types of biological materials, as in samples obtained from the genitourinary tract, biopsies, necropsies, the respiratory tract, ascites, abscess aspirate and ocular material (Table 3).

The most common treatment of individuals potentially parasitized with *B. coli* was an association of tetracycline drugs and nitroimidazole derivatives, represented mainly by tetracycline and metronidazole. In addition, more than 20% of parasitized individuals included in the studies underwent a test of cure, i.e., the laboratory tests were repeated after their pharmacological treatment. However, total recovery, i.e., clinical and/or parasitological cure, was only reported for 14.9% of infected patients. Fourteen (13.6%) of the articles described human cadaver studies and/or the outcome of death during a clinical case, representing 18 people (Table 3). Tables 4 and 5 summarize the information retrieved from the eligible scientific articles.

4. Discussion

The search for scientific articles in the aforementioned databases yielded 1230 studies that addressed the proposed theme and that were available for complete download. After removing repetitions, 815 articles were left. However, not all of them met the inclusion criteria, and only 104 articles proved to be eligible. Unfortunately, an epidemiological article (Esteban et al., 1997) had to be removed from the analysis, since the data on *B. coli* in this work were also included in a more complete and specific version about the protozoan by Esteban and collaborators published in 1998. The later version was thus included in this review.

In general, most of the articles on human balantidiasis included in this study were medical reports of clinical cases, which represented 72.8% of the scientific works analyzed here. Surprisingly, very few articles were retrieved concerning epidemiological studies focusing exclusively on balantidiasis. This focus was only identified in the articles, who used coproparasitological techniques to analyze the frequency of *B. coli* among schoolchildren of the Aymara ethnic group in the Bolivian Altiplano and in Paraná, Brazil (Esteban et al., 1998; Barbosa and Pavanelli, 2020). In addition to the epidemiological study carried out in Bangladesh, in which *B. coli* was investigated in fecal samples from people of different age groups (Hasan et al., 2015). The other epidemiological articles addressed research on intestinal parasites infection and on secondary data, as was done by Zarbaliyev and Celik (2018), who detected the protozoan in data retrieved from medical records of patients that underwent an appendectomy in Turkey. The low number of articles on human balantidiasis retrieved in this review is in line with the findings of Hernández and Rivera (1991). These authors pointed out that the literature on human balantidiasis is very scanty for two fundamental reasons: the first is due to the low prevalence of the parasite in humans, and the second concerns the low number of publications that usually focus on clinical case reports of symptomatic patients. The editors of many journals are often wary of accepting articles on clinical cases, which are therefore published in the form of short

Table 2
Absolute and relative values of scientific articles and individuals potentially infected with *Balantioides coli* in relation to retrieved general, infection and diagnose information.

Information	Articles analyzed (*n* = 103)		Number of case reports (*n* = 75)		Number of epidemiological studies (*n* = 28)		Number of people infected with *Balantioides coli* (*n* = 997)	
Age	n	%	n	%	N	%	n	%
Child	20	19.4	14	18.7	6	21.4	87	8.7
Teenager	7	6.8	7	9.3	0	0	7	0.7
Adult	44	42.7	42	56	2	7.1	49	4.9
Elderly	23	22.3	22	29.3	1	3.6	26	2.6
Many kind of people without specifying the age of positivity	17	16.5	1	1.3	16	57.1	619	62.1
Not reported the age of people inclueded in study	4	3.9	1	1.3	3	10.7	209	21
Comorbidity/concomitant infection								
Yes	51	49.5	40	53.3	11	39.3	214	21.5
Not reported	58	56.3	38	50.7	20	71.4	783	78.5
Use of alcohol								
Yes	6	5.8	6	8	0	0	6	0.6
No and Not reported	97	94.2	69	92	28	100	991	99.4
Infection								
Intestinal	73	70.9	46	61.3	27	96.4	965	96.8
Extraintestinal	26	25.2	25	33.3	1	3.6	27	2.7
Instestinal e extraintestinal	5	4.9	5	6.7	0	0	5	0.5
Organ or tissue potentially colinized in atypical infections								
Appendix	3	2.9	2	2.7	1	3.6	3	0.3
Liver	1	1	1	1.3	0	0	1	0.1
Eyeball	2	1.9	2	2.7	0	0	2	0.2
Peritonium	1	1	1	1.3	0	0	1	0.1
Lungs	5	4.9	5	6.7	0	0	5	0.5
Genitourinary tract	16	15.5	15	20	1	3.6	17	1.7
Vertebra	1	1	1	1.3	0	0	1	0.1
Appendix and Peritonium	2	1.9	2	2.7	0	0	2	0.2
Intestine and Lungs	3	2.9	3	4	0	0	3	0.3
Gallblader	1	1.0	1	1.3	0	0	1	0.1
Apendix, lungs, liver and peritonium	1	1.0	1	1.3	0	0	1	0.1
Type of infection								
Symptomatic	82	79.6	73	97.3	9	32.1	314	31.5
Asymptomatic	2	1.9	0	0	2	7.1	31	3.1
Not reported	22	21.4	4	5.3	18	64.3	652	65.4
Clincal manifestation								
Colic/abdominal pain	37	35.9	33	44	4	14.3	48	4.8
Dysentery	31	30.1	29	38.7	2	7.1	128	12.8
Diarrhea	31	30.1	25	33.3	6	21.4	44	4.4
Tenesmus	8	7.8	8	10.7	0	0	96	9.6
Difficulty in walking	1	1	1	1.3	0	0	1	0.1
Oliguria	1	1	1	1.3	0	0	1	0.1
Dysuria	6	5.8	4	5.3	2	7.1	6	0.6
Vaginal itching	1	1	1	1.3	0	0	1	0.1
Dyspnea	8	7.8	8	10.7	0	0	8	0.8
Hemoptise	2	1.9	2	2.7	0	0	2	0.2
Pain in the right hypochondrium	2	1.9	2	2.7	0	0	2	0.2
Distention of the abdomen	2	1.9	2	2.7	0	0	2	0.2
Red eye	2	1.9	2	2.7	0	0	2	0.2
Photophobia	1	1	1	1.3	0	0	1	0.1
Foreign body sensation	2	1.9	2	2.7	0	0	2	0.2
Swelling of both lower limbs	1	1	1	1.3	0	0	1	0.1
Fecal sample collected								
Yes	85	82.5	58	77.3	27	96.4	972	97.5
Not collected/not reported	19	18.4	18	24	1	3.6	25	2.5
Use of chemical preservative in the fecal sample								
With preservative	8	7.8	1	1.3	7	25	538	54
Not reported	51	49.5	40	53.3	11	39.3	245	24.6
Not collected	19	18.4	18	24	1	3.6	25	2.5
Without preservative	26	25.2	17	22.7	9	32.1	189	19
Quantity of stool samples collected								
One	14	13.6	2	2.7	12	42.9	98	9.8
Two	10	9.7	8	10.7	2	7.1	24	2.4
Three	12	11.7	11	14.7	2	7.1	16	1.6
Five	2	1.9	2	2.7	0	0	3	0.3
Six	2	1.9	1	1.3	1	3.6	2	0.2
Not collected	19	18.4	18	24	1	3.6	25	2.5
Not reported	49	47.6	37	49.3	11	39.3	829	83.1
Laboratory coproparasitological techniques								
Sedimentation	7	6.8	3	4	4	14.3	24	2.4
Direct exam	18	17.5	13	17.3	5	17.9	171	17.2
Flotation	1	1	0	0	1	3.6	9	0.9
Stool cuture	1	1	1	1.3	0	0	1	0.1

(*continued on next page*)

Table 2 (*continued*)

Information	Articles analyzed (*n* = 103)		Number of case reports (*n* = 75)		Number of epidemiological studies (*n* = 28)		Number of people infected with *Balantioides coli* (*n* = 997)	
Age	n	%	n	%	N	%	n	%
Stoll counting technique	1	1	0	0	1	3.6	10	1
Permanent staining of fecal material	1	1	1	1.3	0	0	1	0.1
Direct exam and sedimentation	7	6.8	2	2.7	5	17.9	456	45.7
Direct exam and staining permanent	1	1	1	1.3	0	0	1	0.1
Sedimentation and flotation	2	1.9	0	0	2	7.1	11	1.1
Sedimentation and permanent staining	1	1	0	0	1	3.6	1	0.1
Direct exam, sedimentation and staining permanent	3	2.9	0	0	3	10.7	23	2.3
Sedimentation. flotation and thermohydrotropism	1	1	0	0	1	3.6	1	0.1
Direct exam, staining permanent and cellophane tape	1	1	0	0	1	3.6	112	11.2
Direct exam, flotation, sedimentation and coproculture	1	1	1	1.3	0	0	1	0.1
Sedimentation, flotation, thermohydrotropism and staining permanent	1	1	0	0	1	3.6	1	0.1
Not reported	38	36.9	36	48	2	7.1	149	14.9
Not collected	19	18.4	18	24	1	3.6	25	2.5

Table 3
Absolute and relative values of scientific articles and individuals potentially infected with *Balantioides coli* in relation to retrieved diagnose and treatment information.

Information	Articles analyzed (*n* = 103)		Number of case reports (*n* = 75)		Number of epidemiological studies (*n* = 28)		Number of people infected with *Balantioides coli*(*n* = 997)	
Diagnosis in feces	n	%	n	%	n	%	n	%
Trophozoite	25	24.3	24	32	1	0.3	224	22.5
Cyst	8	7.8	3	4	5	1.4	45	4.5
Trophozoite and cyst	7	6.8	6	8	1	0.3	7	0.7
Not reported	20	19.4	4	5.3	21	5.9	671	67.3
Negative	24	23.3	23	30.7	1	0.3	25	2.5
Not collected	19	18.4	18	24	1	0.3	25	2.5
Diagnosis in the genitourinary tract								
Trophozoite	12	11.7	11	14.7	1	0.3	13	1.3
Trophozoite and cyst	4	3.9	4	5.3	0	0	4	0.4
Diagnosis in biopsy/Histopathology								
Trophozoite	14	13.6	14	18.7	0	0	15	1.5
Trophozoite and cyst	1	1	1	1.3	0	0	1	0.1
Not reported	1	1	0	0	1	0.3	2	0.2
Diagnosis in necropsy/Histopathology								
Trophozoite	9	8.7	9	12	0	0	12	1.2
Diagnosis in ascites								
Trophozoite	1	1	1	1.3	0	0	1	0.1
Diagnosis in bronchoalveolar lavage								
Trophozoite	6	5.8	6	8	0	0	6	0.6
Diagnosis in liver abscess								
Trophozoite	1	1.0	1	1.3	0	0	1	0.1
Diagnosis in ocular material								
Trophozoite	2	1.9	2	2.7	0	0	2	0.2
Drug Treatment								
Tetracyclines	7	6.8	7	9.3	0	0	7	0.7
Tetracyclines and Nitroimidazoles	9	8.7	9	12	0	0	118	11.8
Tetracyclins and other drugs	5	4.9	5	6.7	0	0	5	0.5
Nitroimidazoles	19	18.4	17	22.7	2	0.6	21	2
Nitroimidazoles and other drugs	9	8.7	9	12	0	0	9	0.9
Other drugs and treatments	18	17.5	18	24	0	0	117	11.7
Not reported	39	37.9	13	17.3	26	7.3	716	71.8
Unrealized	2	1.9	2	2.7	0	0	4	0.4
Repetition of diagnostic after treatment								
Realized	37	35.9	37	49.3	1	0.3	244	24.5
Unrealized	15	14.6	15	20	0	0	19	2
Not reported	54	52.4	27	36	27	7.6	734	73.6
Clinical outcome								
Recovered	51	49.5	50	66.7	1	0.3	149	14.9
Death	14	13.6	14	18.7	0	0	18	1.8
Not reported	43	41.7	16	21.3	27	7.6	830	83.2

notes, often in Spanish or Portuguese when Latin countries are involved. These publications end up not being read by the wider scientific community, whose lingua franca is English. This predominance of clinical case reports in other languages, which has been previously reported, was clearly evident in this systematic review.

The frequency of individuals potentially infected with *B. coli* (997/ 24,999 – 3.98%) evidenced in this review differed from the worldwide prevalence of 1% of human balantidiasis postulated by Schuster and Ramirez-Ávila in their review of 2008. However, it should be noted that this frequency cannot be considered a prevalence index, since such rates are usually extrapolated from medical reports published on the platforms of public health institutions. Moreover, although a variety of descriptors in different languages were used in our search, only a small fraction of the number of published articles were available for retrieval from the databases listed earlier herein. However, because this is a highly neglected parasite, the frequency shown in this review can be

Table 4
Systematic review of general information retrieved from clinical cases and from epidemiological studies that reported infections by *Balantioides coli* in humans.[e]

Number	Year	Authors	Country	Continent	Study	Age (Sample group)	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Proximity to pigs and/or their excreta
1	1910	Bel and Couret	USA	North America	CR	Adult	1	1	Tuberculosis	Y	Y
2	1918	Debuys	USA	North America	CR	Child	1	1	N	N	Y
3	1919	Mason	China	Asia	CR	Adult	1	1	Malaria	N	Y
4	1923	Greene and Scully	USA	North America	CR	Child (1), Teenager (1), Adult (1) and Elderly (1)	4	4	N (4)	N (4)	N (4)
5	1931	Little	Canada	North America	CR	Elderly	1	1	Cerebral arteriosclerosis	N	N
6	1935	Banik	India	Asia	CR	Elderly	1	1	N	N	Y
7	1940	Hummel	USA	North America	CR	Adult	1	1	*Entamoeba histolytica*	N	N
8	1943	Delanney and Beahm	USA	North America	CR	Adult	1	1	N	N	N
9	1947	Shun-Shin	Mauritius	Africa	CR	Adults (2), Children (6), Teenager (1) and Elderly (1)	10	10	N(4), *Trichuris trichiura* (1) and *Ascaris lumbricoides*(6)	N (10)	N (10)
10	1948	Miller and Peck	India	Asia	CR	Adult	1	1	N	N	N
11	1952	McCarey	Iran	Asia	CR	Adults (2), Children (6), Teenager (1), Elderly (1) and N (77)	87	87	N(87)	N	Hadn't contact with pigs (87)
12	1953	Elliot and Hotson	Canada	North America	CR	Adult	1	1	Psychiatric disorders	N	Y
13	1955	Mejia	Canada	South America	CR	Elderly	1	1	Neoplasm	N	N
14	1955	Areán and Koppisch	Puerto Rico	Central America	CR	Adults (2) and Children (3)	5	5	N (3), Tuberculosis (1), *Ascaris lumbricoides*and *Trichuris trichiura*(1)	N (5)	N (5)
15	1960	Woody and Woody	USA	North America	CR	Child	1	1	N	N	Hadn't contact with pigs
16	1967	Wenger	Venezuela	South America	CR	Teenager	1	1	N	N	N
17	1970	Baskerville et al.	Canada	North America	CR	Adult	1	1	Psychiatric disorders	N	N
18	1970	Lerman et al.	Hawaii - USA	North America	CR	Adult	1	1	N	N	N
19	1973	Walzer et al.	Micronesia/ Truk - USA	Oceania	CR	Children, Teenagers, Adults and Elderlies	110	110	N (110)	N (110)	Y (110)
20	1977	Rees and Shelley	Brazil	South America	CR	Adult - indians	1	1	*Ascaris lumbricoides* and *Trichuris trichiura*	N	Y
Number	Year	Authors	Country	Continent	Study	Age/Sample group	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Contact with pigs and their excrement
21	1980	Moraleda et al.	Chile	South America	CR	Child	1	1	Malnutrition and *Trichuris trichiura*	N	Hadn't contact with pigs
22	1981	Vasconcelos	Brazil	South America	E	Child	110	1	N	N	N
23	1984	Dorfman et al.	Venezuela	South America	CR	Teenager	1	1	N	N	Y
24	1989	Ladas et al.	Greece	Europe	CR	Elderly	1	1	Aspergillosis	N	Hadn't contact with pigs
25	1991	Coimbra Jr and Santos	Brazil	South America	E	Children, teenagers, adults and elderlies - indians	173	5	N (5)	N (5)	Y (5)
26	1991	Dodd	USA	North America	CR	Teenager	1	1	N	N	N
27	1991	Pamo et al.	Peru	South America	CR	Elderlies(4)	4	4	N (3) and *Trichuris trichiura* (1)	N (4)	N (4)
28	1991	Pinheiro and Lima	Brazil	South America	CR	Elderly	1	1	Malnutrition, Chagas disease and Chronic obstructive pulmonary disease	N	Y
29	1991	Hernández et al.	Costa Rica		CR	Child(1) and adult(1)	2	2	N (2)	N (2)	Y (2)

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Table 4 (*continued*)

Number	Year	Authors	Country	Continent	Study	Age/Sample group	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Contact with pigs and their excrement
				Central America							
30	1993	Saborío et al.	Costa Rica	Central America	CR	Child - indians	1	1	N	N	Y
31	1996	Borda et al.	Argentina	South America	E	Children - students	207	1	N	N	N
32	1997	Giacometti et al.	Italy	Europe	E	Adults and elderlies - Institutions that assist patients with mental disorders	238	1	Psychiatric disorders	N	N
33	1998	Clyti et al.	French Guiana	South America	CR	Adult	1	1	Histoplasmosis and HIV	N	Y
34	1998	Esteban et al.	Bolívia	South America	E	Children and teenagers - students - collection in schools - indians	2,124	26	N (26)	N (26)	Y (26)
35	1998	Houssaye et al.	French Polynesia	Oceania	CR	Elderly	1	1	Diabetes	N	N
36	1999	Vásquez and Vidal	Peru	South America	CR	Elderly	1	1	N	N	Y
37	2000	Cano Rosales et al.	Peru	South America	CR	Child	1	1	N	N	Hadn't contact with pigs
38	2002	Kaur et al.	India	Asia	E	Children and teenagers admitted to the hospital complaining of diarrhea	127	3	N(3)	N (3)	N (3)
39	2003	Anargyrou et al.	Greece	Europe	CR	Adult	1	1	Chronic leukemia	N	Hadn't contact with pigs
40	2003	Cermeño et al.	Venezuela	South America	CR	Adult	1	1	HIV	N	N
41	2003	Sharma and Harding	Canada	North America	CR	Adult	1	1	Diabetes	N	Y-Organic Farmer
42	2003	Urbina et al.	Colombia	South America	E	Children (2) who had a history of diarrhea conducted in hospital	253	2	N (2)	N (2)	N (2)
43	2003	Vasilakopoulou et al.	Greece	Europe	CR	Elderly	1	1	Anal neoplasm and Diabetes	N	Hadn't contact with pigs
Number	Year	Authors	Country	Continent	Study	Age/Sample group	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Contact with pigs and their excrement
44	2004	Arcoverde et al.	Brazil	South America	E	Adults and elderlies	110	1	HIV	N	N
45	2004	Coutinho et al.	Brazil	South America	CR	Child	1	1	Varicella	N	Y
46	2004	Ferry et al.	France	Europe	CR	Adult	1	1	N	Y	Y, Worked in pig slaughterhouse
47	2004	Yazar et al.	Turkey	Europe and Asia	CR	Adult	1	1	Non-Hodgkin's lymphoma	N	Hadn't contact with pigs
48	2005	Gezuele et al.	Uruguay	South America	CR	Adult	1	1	N	N	N
49	2005	Marques et al.	Brazil	South America	E	Children, teenagers, adults and elderlies	9,024	1	N	N	N
50	2006	Agapov	Russia	Asia	CR	Teenager	1	1	N	N	N
51	2006	Cheng - Ng et al.	Venezuela	South America	CR	Child - indians	1	1	*Trichuris trichiura* and Hookworm	N	Y
52	2007	Cristescu and Reka	USA	North America	CR	Adult	1	1	*Trichuris trichiura*	N	N
53	2007	Umesh	India	Asia	CR	Adult	1	1	Candidiasis	N	N
54	2008	Udeh et al.(a)	Nigeria	Africa	E	NR	900	1	HIV/AIDS	N	N
55	2010	Koopowitz et al.	England	Europe	CR	Adult	1	1	N	N	Y,Played rugby on a lawn fertilized with pig feces
56	2010	Maino et al.	Italy	Europe	CR	Adult	1	1	Non-Hodgkin's lymphoma	N	Hadn't contact with pigs
57	2011	Carlos and Hilda	Costa Rica	Central America	CR	Child - indians	1	1	N	N	N
58	2011	Liyanage et al.	Sri Lanka	Asia	CR	Adult	1	1		N	N

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Table 4 (*continued*)

Number	Year	Authors	Country	Continent	Study	Age/Sample group	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Contact with pigs and their excrement
59	2011	Poudyal et al.	Nepal	Asia	CR	Adult	1	1	Pemphigus vulgaris and Diabetes Hookworm, *Giardia duodenalis* and *Entamoeba coli*	N	Hadn't contact with pigs
60	2012	Figueiredo et al.	Brazil	South America	CR	Adult	1	1	HIV	N	Hadn't contact with pigs
61	2013	Bandyopadhyay et al.	India	Asia	CR	Elderly	1	1	N	N	Hadn't contact with pigs
62	2013	Bellanger et al.	France	Europe	CR	Adult	1	1	N	N	Hadn't contact with pigs
63	2013	Boonjaraspinyo	Thailand	Asia	E	Children, teenagers, adults and elderlies - epidemiological study conducted house by house	253	1	N	N	N
64	2013	Dhawan et al.	India	Asia	CR	Elderly	1	1	N	Y	Hadn't contact with pigs
65	2013	Majumdar et al.	India	Asia	CR	Adult	1	1	N	N	N
66	2014	Karuna and Khadanga	India	Asia	CR	Elderly	1	1	Diabetes and Chronic kidney disease	N	N
67	2014	Khanduri et al.	India	Asia	CR	Adult	1	1	N	N	Hadn't contact with pigs
68	2015	Biolchi et al.	Brazil	South America	E	Children and teenagers - urban and rural students	109	1	N	N	Y
69	2015	Feleke	Ethiopia	Africa	E	N	710	19	*Trichuris trichiura* and *Entamoeba histolytica*	N (19)	N (19)
70	2015	Maa Hasan et al.	Bangladesh	Asia	E	Children, teenagers, adults and elderlys	150	10	N (10)	N (10)	N (10)
71	2015	McLeod et al.	Australia	Oceania	CR	Child - indians	1	1	Hymenolepiasis	N	Y
72	2015	Pinheiro et al.	Brazil	South America	CR	Adult	1	1	N	N	N
73	2015	Poloni et al.	Brazil	South America	CR	Adult	1	1	Obstructive uropathy	N	N
74	2015	Sandoval et al.	Panama	Central America	E	Children, teenagers, adults and elderlies - Health Units	1,123	9	N (9)	N (9)	N (9)
75	2015	Soleimanpour et al.	Iran	Asia	CR	Adult	1	1	Diabetes, Hypothyroidism and Drug addict	Y	Hadn't contact with pigs
76	2016	Hazarika et al.	India	Asia	CR	Adult	1	1	N	N	N
77	2016	Ikpeama et al.	Nigeria	Africa	E	Children, teenagers and adults	398	10	HIV/AIDS	N	N
78	2016	Kapur et al.	India	Asia	CR	Adult	1	1	N	Y	N
79	2016	Kaur and Gupta	India	Asia	CR	Elderly	1	1	Chronic obstructive pulmonary disease	N	Hadn't contact with pigs
80	2016	Kumar et al.	India	Asia	CR	Adult	1	1	Tuberculosis	Y	Hadn't contact with pigs
81	2016	Mane et al.	India	Asia	CR	Elderly	1	1	*Escherischia coli* infection in the genitourinary tract	N	Hadn't contact with pigs
82	2016	Zavala et al.	Mexico	North America	E	Children - rural schoolchildren	296	37	N (37)	N (37)	N (37)
83	2017	Albuquerque and Souza	Brazil	South America	E	Teenagers, Adults and elderlies	50	6	People with intellectual and/ or multiple special needs (6)	N (6)	N (6)
84	2017	Gupta et al.	India	Asia	CR	Adults (2)	2	2	N (2)	N (2)	N (2)
85	2017	Mayuri and Mayuri	India	Asia	CR	Adult	1	1		N	N

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Table 4 (*continued*)

Number	Year	Authors	Country	Continent	Study	Age/Sample group	Sample number	P	Comorbidity/ concomitant infection	Use of alcohol	Contact with pigs and their excrement
									Pulmonary arterial hypertension and complete heart block		
86	2018	Bratta and Quintero	Venezuela	South America	CR	Adult	1	1	Diabetes mellitus	N	N
87	2018	Khurana et al.	India	Asia	E		33	2	*Trichomonas vaginalis*(2)	N (2)	N (2)
88	2018	Tanja et al.	Slovenia	Europe	CR	Elderly	1	1	Psoriasis, diabetes mellitus type II, hypertension, dyslipidemia, fatty liver disease, left breast carcinoma and Schawnnoma of the stomach	N	Y (pig farmer)
89	2018	Zarbaliyev and Celik	Turkey	Europe	E	Adults(2) Retrospective study - medical record	97	2	N (2)	N (2)	Y (1), Hadn't contact with pigs (1)
90	2019	Alomashi and Al-Shabbani	Iraq	Asia	E	N	974	112	Anaemia (974), *Entamoeba histolytica* (28), *Giardia duodenalis* (14), *Cryptosporidium* sp. (14), *Ascaris lumbricoides* (14), *Enterobius vermicularis* + *Giardia duodenalis* (14)	N	N (112)
91	2019	Feleke et al.	Ethiopia	Africa	E	Children, teenagers, adults and elderlies	4,436	411	N (411)	N (411)	N (411)
92	2019	Gomez Hinojosa et al.	Peru	South America	CR	Elderly	1	1	N	N	Y
93	2019	Khurana et al.	India	Asia	CR	Elderly	1	1	N	N	N
94	2019	Udeh et al. (b)	Nigeria	Africa	E	Teenagers and adults	1041	14	HIV/AIDS (10) and N(4)	N	N (14)
95	2020	Aninagyei et al.	Ghana	Africa	E	Children, teenagers, adults and elderlies	538	9	*Entamoeba histolytica*(4) and N (5)	N (9)	N (9)
96	2020	Bahaa Alaa	Iraq	Asia	E	Children (8)	100	8	N (8)	N (8)	N (8)
97	2020	Barbosa and Pavanelli	Brazil	South America	E	Children - rural schoolchildren (10)	42	10	*Entamoeba coli*(2) and N (8)	N	N(10)
98	2020	Boy et al.	Paraguay	South America	E	Children (2)	40	2	N (2)	N (2)	N (2)
99	2020	Joshi and Scarff	USA	North America	CR	Elderly	1	1	N	N	N
100	2020	Kumar et al.	India	Asia	E	Children and teenagers	1,052	1	N	N	N
101	2020	Martviset et al.	Thailand	Asia	CR	Adult	1	1	Systemic lupus erythematosus	No	Hadn't contact with pigs (1)
102	2021 (2020 year to accept)	Pérez-Hernández et al.	Colombia	South America	CR	Adult	1	1	N	N	N
103	2020	Yu et al.	China	Asia	CR	Elderly	1	1	N	N	Y

[e] CR: Case reported; E: Epidemiological, P: Frequency of positive people; N: not reported or No.

considered the most up-to-date average that has been published to date about possible cases of human balantidiasis.

Most of the articles retrieved in this review were published in the most recent time interval, i.e., 1998–2020, highlighting the epidemiological studies, period of years and studies in which the largest proportion of the human balantidiasis event was observed through meta-analysis. This was expected, since more recent studies are usually available online in scientific journals, which is not always the case with older articles; hence, this data requires careful analysis. It's important to note, the higher number of infected people found in this time interval (1998–2020) is directly associated with the epidemiological study in Etiopia by Feleke et al. (2019). In this article, the authors, through a large sample panel, that is, 4436 participants, researched parasites in family members of patients known to be infected with intestinal parasites, and 411 individuals potentially infected with *B. coli* were identified.

The high number of case reports of infected individuals was also found in the study within the time interval of 1954–1975 is directly

Table 5
Systematic review of information retrieved from different databases on clinical manifestations, diagnosis and treatment of clinical cases and epidemiological studies that reported infections with *Balantioides coli* in humans.[a]

Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/ With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
1	Bel and Couret	1910	1	1	Y	No	Diarrhea, Abdominal pain, Tenesmus, Dysentery and Distention of the abdomen	Y/N/N	Coproparasitological N (+), necropsy histopathology (+)	Trophozoite	N	N	Death
2	Debuys	1918	1	1	Y	No	Diarrhea and Dysentery	Y/Without preservative/One sample	Coproparasitological N(+)	Trophozoite	N	N	N
3	Mason	1919	1	1	Y	No	Dysentery	Y/N/Two samples	Coproparasitological N (+)	N	Plant oil	Y	Recovered
4	Greene and Scully	1923	4	4	Y(4)	No(4)	Colic(1), Dysentery(2), Diarrhea(1) and Constipation (1)	Y/N/N (4)	Coproparasitological N (+4)	N (4)	Milk (4)	Y (4)	Recovered (4)
5	Little	1931	1	1	Y	No	Colic and Dysentery	Y/N/N	Coproparasitological Permanent staining (+)	Trophozoite	Plant oil	N	Recovered
6	Banik	1935	1	1	Y	No	Colic and Dysentery	Y/N/N	Coproparasitological Direct exam (+)	Trophozoite	Magnesium Sulfate and Emetine	Y	Recovered
7	Hummel	1940	1	1	Y-Granuloma in the rectum	No	Abdominal pain and Dysentery	Not collected	Sigmoidoscopy intestinal ulcer biopsy (+)	Trophozoite	Iodoquinol	N	N
8	Delanney and Beahm	1943	1	1	Y	No	Dysentery	Not collected	Sigmoidoscopy rectal lesion biopsy (+)	Trophozoite	Carbasone, Plant oil and Iodoquinol	Y	Recovered
9	Shun-Shin	1947	10	10	Y(10)	N(10)	Dysentery(9), Weakness (1), Colic (1), Diarrhea (1) and Tenesmus (2)	Y/N/N (3), Y/N/Three samples (3), Y/N/Five samples (2), Y/N/Two samples (2)	Coproparasitological N (+10)	N (9), Trophozoite (1)	Mepacrine and Opium Bismuth (1), Mercury Biodide (9) and Plant Oil (1)	N (1), Unrealized (1) and Y (8)	Death (1) and Recovered (9)
10	Miller and Peck	1948	1	1	Y	No	Dysentery	Not collected	Necropsy hispathology (+)	Trophozoite	Unrealized	Unrealized	Death
11	McCarey	1952	87	87	Y(87)	No	Dysentery and Tenesmus (87)	Y/N/N (87)	Coproparasitological N (+87)	Trophozoite (87)	Acetarsol (87)	Y (87)	Recovered (87)
12	Elliot and Hotson	1953	1	1	Y	No	Colic and Dysentery	Y/N/N	Coproparasitological Direct exam (+)	Trophozoite	Carbasone and Sulfaguanidine	Y	Recovered
13	Mejia	1955	1	1	No	Genitourinary tract	Vaginal itching	Y/N/N	Coproparasitological N(-), Papa Nicolau, Direct exam of genital fluid (+) and endoscopy	Trophozoite and Cyst	Topical antiseptics	N	N
14	Areán and Koppisch	1956	5	5	Y(5)	No(5)	Dysentery (2), N (1), Abdominal pain (2)	Not collected (5)	Necropsy histopathology (+3), biopsy(+2)	Trophozoite (5)	Unrealized (3) and Surgical (2)	Unrealized (3) and N (2)	Deaths (3), Recovered (1) and N (1)
15	Woody and Woody	1960	1	1	Y	No	Diarrhea	Y/Without preservative/Two samples	Coproparasitological Direct exam (+)	Trophozoite	Carbasone	Y	Recovered
16	Wenger	1967	1	1	Y-appendix	Lungs, liver and peritoneum	Pain in the right hypochondrium and Diarrhea	Not collected	Necropsy histopathology(+)	Trophozoite	Surgical	Unrealized	Death
17	Baskerville et al.	1970	1	1	Y	No	Abdominal pain	Not collected	Necropsy histopathology(+)	Trophozoite	Surgical	Unrealized	Death
18	Lerman et al.	1970	1	1	Y	No	Diarrhea	Y/Without preservative/N	Coproparasitological Direct exam (+)	Trophozoite	Tetracycline and Diodoquinol	N	Recovered
19	Walzer et al.	1973	110	110	Y(110)	N(110)	Gastrointestinal symptoms not detailed (110)	Y/Without preservative/N (110)	Coproparasitological Direct exam (+110)	Trophozoite (110)	Tetracycline and Metronizadole (110)	Y	N (110)
20	Rees and Shelley	1977	1	1	Y	No	Abdominal pain and Dysentery	Y/Without preservative/Three samples	Coproparasitological Direct exam and sedimentation with MIF (+)	Trophozoite	Chlortetracycline	Unrealized	N

Number Authors Year P Intestinal Extraintestinal Clinical Manifestation Laboratory technique performed Detected form Treatment performed

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Table 5 (*continued*)

Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
21	Moraleda et al.	1980	1	1	Y	No	Abdominal pain, Diarrhea and Dysentery	Y/Without preservative/Three samples	Coproparasitological Teleman (+) and endoscopy (-)	Trophozoite	Tetracycline and Metronizadole	Y	Recovered
22	Vasconcelos	1981	110	1	Y	No	Diarrhea	Y/N/N	Coproparasitological Direct exam (+)	N	N	N	N
23	Dorfman et al.	1984	1	1	Y-appendix	Peritoneum	Abdominal pain and Diarrhea	Not collected	Appendix biopsy (+)	Trophozoite	Surgery and drainage of the peritoneum	Unrealized	Death
24	Ladas et al.	1989	1	1	Y	Lungs	Asthmatic crises, Colic, Dysentery and Dyspnea	Y/Without preservative/Two samples	Coproparasitological N (-), X-ray (+), biopsy of rectal polyp and lung mass(+)	Trophozoite	Doxycycline	Y-Image	Recovered
25	Coimbra Jr and Santos	1991	173	5	Y(5)	No(5)	Asymptomatic (5)	Y/Without preservative/N (5)	Coproparasitological Sedimentation (+5)	N (5)	N (5)	N (5)	N(5)
26	Dodd	1991	1	1	Y-appendix	No	Abdominal pain	Not collected	Appendix biopsy (+)	Trophozoite	Surgical	Unrealized	N
27	Pamo et al.	1991	4	4	Y(4)	No(4)	Diarrhea (2), Dysentery (2), Dysuria (1), Abodminal pain (2) and Tenesmus (2)	Y/N/N (3), Not collected (1)	Coproparasitological N (+3), Necropsy histopathology (+1)	Trophozoite (4)	Tetracycline (1), N (1), Chloramphenicol and Aminosidine (1), Doxycycline and Albendazole (1)	N (2), Unrealized (2)	N (1), Death (2), Recovered (1)
28	Pinheiro and Lima	1991	1	1	Y	N	Colic and Dysentery	Not collected	Necropsy histopathology (+)	Trophozoite	N	N	Death
29	Hernández et al.	1993	2	2	Y(2)	No(2)	N(2)	Not collected (2)	Necropsy Histopathology (+2)	Trophozoite(2)	N(2)	Unrealized (2)	Death (2)
30	Saborío et al.	1993	1	1	Y	No	Colic, Dysentery and Tenesmus	Not collected	Anal biopsy (+)	Trophozoite	Tetracycline and Chloramphenicol	Unrealized	Recovered
31	Borda et al.	1996	207	1	Y	No	N	Y/Without preservative/Six samples	Coproparasitological Direct exam, Sedimentation and permanent staining (+)	N	N	N	N
32	Giacometti et al.	1997	238	1	Y	No	Abdominal pain, Diarrhea, Dysentery and Pruritus	Y/Without preservative/Three samples	Coproparasitological Direct exam and Formol-ether sedimentation (+)	Cyst	N	N	N
33	Clyti et al.	1998	1	1	Y	No	Abdominal pain and Diarrhea	Y/N/Three samples	Coproparasitological Direct exam (+)	Trophozoite	Doxycycline	Y	Recovered
34	Esteban et al.	1998	2.124	26	Y(26)	No(26)	Asymptomatic (26)	Y/Without preservative/One sample (26)	Coproparasitological-Kato-Katz, Direct exam with MIF and sedimentation with MIF, Formol-ether sedimentation (26+)	Cyst (22), Trophozoite (3), Trophozoite and Cyst (1)	N (26)	N (26)	N (26)
35	Houssaye et al.	1998	1	1	Y	No	Abdominal pain and Diarrhea	Y/Without preservative/Three samples	Coproparasitological Direct exam (+), colon ulcer biopsy (+) and colonoscopy (+)	Coproparasitological Trophozoite and Cyst, biopsy trophozoite	Metronidazole	Y	Recovered
36	Vásquez and Vidal	1999	1	1	Y	No	Dysentery and Tenesmus	Y/Without preservative/One sample	Coproparasitological Direct exam (+), Permanent staining hematoxilin eosin(+) and Necropsy (+)	Trophozoite	Metronidazole and ceftriaxona	N	Death
37	Cano Rosales et al.	2000	1	1	Y	No	Dysentery	Y/N/N	Coproparasitological N (+), biopsy histopathology	Trophozoite and Cyst	Cotrimoxazole and Amikacin	N	Death
38	Kaur et al.	2002	127	3	Y(3)	No(3)	Diarrhea (3)	Y/N/One sample (3)	Coproparasitological Direct exam, Sedimentation formol eter (3+) and Fast acid staining for coccidia research	N (3)	N (3)	N (3)	N (3)

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Table 5 (*continued*)

								preservative/Quantity of samples				Repetition of diagnostic after treatment	
39	Anargyrou et al.	2003	1	1	No	Lungs	Dyspnea	Y/N/N	Coproparasitological N (-), Direct exam bronchoalveolar lavage (+) and X-ray	Trophozoite	Metronidazole	Y	Recovered
40	Cermeño et al.	2003	1	1	Y	No	Diarrhea	Y/N/N	Coproparasitological Direct exam, Flotation with zinc sulfate, Sedimentatin with formalin - ethyl acetate(+?) and Harada Mori	Cyst	N	N	N
41	Sharma and Harding	2003	1	1	No	Lungs	Hemoptise and Dyspnea	Y/N/Five samples	Coproparasitological N (-), Direct exam bronchoalveolar lavage (+) and Computed Tumography (+)	Trophozoite	Doxycycline	Unrealized	Recovered
42	Urbina et al.	2003	253	2	Y(2)	No	Diarrhea, Dehydration and Colic (2)	Y/Without preservative/One sample (2)	Coproparasitological Direct exam (+2)	N (2)	N (2)	N (2)	N (2)
43	Vasilakopoulou et al.	2003	1	1	Y	Lungs	Diarrhea, Dyspnea and Chest pain	Not collected	Direct exam bronchoalveolar lavage (+) and image examination	Trophozoite	Ciproflaxacin, Imipenem and metronidazole	Unrealized	Recovered
44	Arcoverde et al.	2004	110	1	Y	No	N	Y/N/One sample	Coproparasitological Formol - ether sedimentation (+), Flotation - Sheather, Rugai, Mattos and Brisola and Kinyoun and Tricromo staining	N	N	N	N
45	Coutinho et al.	2004	1	1	Y	No	Diarrhea	Y/N/Three samples	Coproparasitological N (+)	N	Sulfamethoxazole and Metronidazole	Y	Recovered
46	Ferry et al.	2004	1	1	Y	Peritoneum	Dysentery and Colic	Y/N/N	Colonoscopy (necrosis area), biopsy (+), Coproparasitological N (+)	Coproparasitological trophozoite and Cyst, biopsy trophozoite	Doxycycline	Y	Recovered
47	Yazar et al.	2004	1	1	Y	No	Dysentery and Abdominal pain	Y/Without preservative/N	Coproparasitological-Direct exam (+)	Trophozoite	Metronidazole	Y	Recovered
48	Gezuele et al.	2005	1	1	Y	No	Colic and Diarrhea	Y/Without preservative/N	Coproparasitological-Direct exam (+)	Trophozoite and Cyst	Metronidazole	Y	Recovered
49	Marques et al.	2005	9,024	1	Y	No	N	Y/N/N	Coproparasitological Sedimentation Hoffman, Pons and Janer, Flotation-Faust et al. and Baermann - Moraes	N	N	N	N
50	Agapov	2006	1	1	Y	No	Colic, Dysentery and Constipation	Y/N/N	Coproparasitological N (-), Colonoscopy (+)	N	Metronidazole	Y-Image	Recovered
51	Cheng - Ng et al.	2006	1	1	Y	No	Abdominal pain and Diarrhea	Y/Without preservative/N	Coproparasitological Direct exam (+) and Sedimentation with formalin - ether (+)	Trophozoite and Cyst	Metronidazole	Y	Recovered
52	Cristescu and Reka	2007	1	1	Y	No	Dysentery and lower abdominal pain	Y/N/N	Coproparasitological N (-), Colonoscopy and biopsy (+)	Trophozoite	Albendazole and Tetracycline	N	N
53	Umesh	2007	1	1	No	Genitourinary tract	Dysuria and Increased frequency of urination	Y/N/Three samples	Coproparasitological N(-), Urinary sedimentation(+)	Trophozoite	Tetracycline and Metronidazole	Y	Recovered
54	Udeh et al.(a)	2008	900	1	Y	No	N	Y/With preservative/One sample	Coproparasitological - ether sedimentation (+), Modified Ziehl Neelsen and Giemsa staining	N	N	N	N

Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
55	Koopowitz et al.	2010	1	1	No	Lungs	Hemoptise and Dyspnea	Not collected	Bronchial biopsy (+), bronchoalveolar lavage (+) and X-ray (+)	Trophozoite	Oxytetracycline and Metronidazole	N	Recovered
56	Maino et al.	2010	1	1	No	Genitourinary tract	Anuria	Y/N/Six samples		Trophozoite	Metronidazole	Y	Recovered

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Table 5 (*continued*)

									Coproparasitological N(-), Urinary sediment-Four samples from different days(+)				
57	Carlos and Hilda	2011	1	1	Y	No	Diarrhea and Dyspnea	Y/N/N	Coproparasitological-Direct exam (+)	Trophozoite and Cyst	Albendazole and Metronidazole	N	Recovered
58	Liyanage et al.	2011	1	1	Y	No	Dysentery, poor appetite, malaena and perianal pruritus	Y/Without preservation/N	Coproparasitological Stool culture grew (+)	Trophozoite	Doxycycline and ivermectin	Y	Recovered
59	Poudyal et al.	2011	1	1	Y	No	Borborygmy, Abdominal pain and Anorexia	Y/N/Two samples	Coproparasitological Direct exam (+)	Trophozoite	Albendazole and Metronidazole	Y	Recovered
60	Figueiredo et al.	2012	1	1	Y	No	Diarrhea, Abdominal pain and Tenesmus	Y/Without preservative/N	Coproparasitological Spontaneous sedimentation (+)	Trophozoite	N	Y	Recovered
61	Bandyopadhyay et al.	2013	1	1	No	Genitourinary tract	Dysuria, Pelvic pain and Diarrhea	Y/N/Three samples	Coproparasitological N(-) and Urinary Sedimentation (+)	Trophozoite	Metronidazole	Y	Recovered
62	Bellanger et al.	2013	1	1	Y	No	Colic and Diarrhea	Y/N/N	Coproparasitological (+)	Trophozoite	Metronidazole	N	Recovered
63	Boonjaraspinyo	2013	253	1	Y	No	Diarrhea, Dysuria and Increased frequency of urination	Y/With preservative/N	Coproparasitological Formol-ether sedimentation (+)	N	N	N	N
64	Dhawan et al.	2013	1	1	No	Vertebra	Difficulty in walking and Bilateral weakness in the lower limbs	Y/N/N	Coproparasitological N (-), Imaging and vertebra abscess biopsy (+)	Trophozoite	Tetracycline and Metronizadole	Y	Recovered
65	Majumdar et al.	2013	1	1	No	Gallbladder/ Liver	Distention of the abdomen, ascites, weight loss and abdominal pain	Y/N/N	Coproparasitological N(-), Permanent staining of ascites fluid and ultrasound	Trophozoite	Mteronidazole	N	N
66	Karuna and Khadanga	2014	1	1	No	Genitourinary tract	Dysuria	Y/N/Two samples	Coproparasitological N(-), Urinary Sedimentation and Ultrasonography (+)	Trophozoite and Cyst	Tetracycline and Metronidazole	Y	Recovered
67	Khanduri et al.	2014	1	1	No	Genitourinary tract	Malaise, Anorexia and Oliguria	Y/N/Three samples	Coproparasitological N(-) and Urinary Sedimentation (+)	Trophozoite	Metronidazole	Unrealized	N
68	Majumdar et al.	2014	1	1	No	Gallbladder/ Liver	Distention of the abdomen, ascites, weight loss and abdominal pain	Y/N/N	Coproparasitological N(-), Permanent staining of ascites fluid and ultrasound	Trophozoite	Mteronidazole	N	N

Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/ With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
68	Biolchi et al.	2015	109	1	Y	No	N	Y/With preservative/One sample	Coproparasitological Spontaneous sedimentation and centrifuge-flotation	N	N	N	N
69	Feleke	2015	710	19	Y(19)	N	N	Y/N/One sample (19)	Coproparasitological Direct exam, formalin - ether sedimentation and Ziehl - Neelsen	N (19)	N (19)	N (19)	N (19)
70	Maa Hasan et al.	2015	150	10	Y(10)	No (10)	N (10)	Y/N/One sample (10)	Coproparasitological Stoll counting technique (+10)	N (10)	N (10)	N (10)	N (10)
71	McLeod et al.	2015	1	1	Y	N	Diarrhea	Y/N/N	Coproparasitological (+)	Trophozoite	Metronidazole and Praziquantel	Y	Recovered
72	Pinheiro et al.	2015	1	1	No	Eyeball	Red eye, Foreign body sensation, tearing and decreased visual acuity	Not collected	Permanent staining and agar culture of the corneal scrape and lens solution. Direct exam: lens solution (+?)	Trophozoite	N	N	Recovered
73	Poloni et al.	2015	1	1	No	Genitourinary tract	N	Not collected	Urinary sedimentation (+)	Trophozoite and Cyst	N	N	N
74	Sandoval et al.	2015	1,123	9	Y(9)	No (9)	N(9)	Y/With preservative/N (9)	Coproparasitological Flotation with zinc sulfate (+9)	N (9)	N (9)	N (9)	N (9)
75	Soleimanpour et al.	2015	1	1	No	Genitourinary tract	Diarrhea and Constipation	Y/N/N	Coproparasitological N(-), Urinary sedimentation(+)	Trophozoite	Tetracycline and Metronizadole	N	Recovered
76	Hazarika et al.	2016	1	1	No	Eyeball	Blurred vision, Red eye, Foreign body sensation and Photophobia	Y/N/N	Coproparasotiological N (-), Corneal scraping, lens and lens cleaning solution (+)	Trophozoite	Metronidazole, Timolol Maleate and Acetazolamide	Y	Recovered
77	Ikpeama et al.	2016	398	10	Y(10)	N	N	Y/N/N (10)		N	N	N	N

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Table 5 (*continued*)

Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
									Coproparasitological N (+10), Direct exam, Formalin - ether Tecnique, modified acid fast stain				
78	Kapur et al.	2016	1	1	No	Liver	Pain in the right hypochondrium	Not collected	Ultrasonography, Direct exam of liver abscess aspirate (+), Gram staining	Trophozoite	Metronidazole and Amikacin	Y	Recovered
79	Kaur and Gupta	2016	1	1	No	Genitourinary tract	Dyspnea	Y/N/N	Coproparasitological N (-), bronchoalveolar lavage (-), Urinary sedimentation and permanent staining of urine sediment (+)	Trophozoite	N	Unrealized	Death
80	Kumar et al.	2016	1	1	Y	No	Fever, anorexia, abdominal pain and dysentery	Y/Without preservative/N	Coproparasitological (+) Direct exam and Trichrome staining	Trophozoite	Metronidazole	N	Recovered
Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
81	Mane et al.	2016	1	1	No	Genitourinary tract	Polaciuria, Lower abdominal pain on the right side and Diarrhea	Y/N/Three samples	Coproparasitological N (-), Urinary sedimentation(+)	Trophozoite	Tetracycline and Metronizadole	Y	Recovered
82	Zavala et al.	2016	296	37	Y(37)	No (37)	N(37)	Y/N/N (37)	Coproparasitological Direct exam and Kato-Katz (+37)	N (37)	N (37)	N (37)	N (37)
83	Albuquerque and Souza	2017	50	6	Y(6)	No (6)	N(6)	Y/N/One sample (6)	Coproparasitological Spontaneous sedimentation (+6)	N (6)	N (6)	N (6)	N (6)
84	Gupta et al. *	2017	2	2	No (1)*, Y (1)	Genitourinary tract (1)*	Weakness and Diarrhea (1), N (1)	Y/N/N (2)	Coproparasitological N (-1), Coproparasitological-N (+1), Urinary sedimentation (+2)	Urinary sedimentation - Trophozoite (2), Feces Cyst (1)	Metronidazole (1), N (1)	N (2)	N (2)
85	Mayuri and Mayuri	2017	1	1	No	Genitourinary tract	Low urine output, vomiting and breathlessness	Y/N/N	Coproparasitological N (-), Urinary sedimentation and permanent staining with hematoxylin eosin(+)	Trophozoite and Cyst	N	N	N
86	Bratta and Quintero	2018	1	1	No	Lungs	Fever, Cough and Dyspnea	Y/N?/Two samples	Coproparasitological N (-), bronchoalveolar lavage (+) and X-ray	Trophozoite	Metronidazole, sulfamethoxazole and trimethoprim	Unrealized	Recovered
87	Khurana et al.	2018	33	2	No	Genitourinary tract (2)	Dysuria and Polaciuria (1), N (1)	Y/N/N(1), Y/N/Two samples (1)	Corproparasitological N (-2), Urinary sedimentation and permanent staining with Papanicolau and Giemsa, Two samples (+)	Trophozoite (1), Trophozoite and Cyst (1)	Metronidazole (2)	Y (2)	Recovered (2)
88	Tanja et al.	2018	1	1	No	Genitourinary tract (1)	Urinary incontinence	Y/N/N	Corproparasitological N (-1), Urinary sedimentation (+1)	Trophozoite	Metronidazole (1)	Y	Recovered
89	Zarbaliyev and Celik	2018	97	2	Y-appendix (2)	No (2)	Abdominal pain (2)	Not collected (2)	Appendix biopsy (+2)	N (2)	Surgical and Metronidazole (2)	N (2)	N (2)
90	Alomashi and Al-Shabbani	2019	974	112	Y (112)	No	N (211)	Y/With preservative/N (112)	Coproparasitological Direct exam with iodine, Ziehl Neelsen staining and cellophane tape method	N (112)	N	N	N
Number	Authors	Year	Sample number	P	Intestinal	Extraintestinal	Clinical Manifestation	Fecal sample collected/With or without preservative/Quantity of samples	Laboratory technique performed	Detected form	Treatment performed	Repetition of diagnostic after treatment	Clinical outcome
91	Feleke et al.	2019	4,436	411	Y (411)	No	N (411)	Y/With preservative/N (411)	Coproparasitological Direct exam and ether sedimentation (+411)	N (411)	N (411)	N (411)	N (411)
92	Gomez Hinojosa et al.	2019	1	1	Y	No	Colic, Vomit, Nausea and Dysentery	Y/Without preservation/N	Coproparasitological Direct exam (+), biopsy histopathology (+)	Trophozoite	Metronidazole, Tetracycline and Surgical	N	Death
93	Khurana et al.	2019	1	1	No	Genitourinary tract (1)		Y/N/Two samples	Coproparasitological N (-), Sedimentation urinary (+)	Trophozoite	Metronidazole	Y	Recovered

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Table 5 (*continued*)

							Increased urinary frequency and burning micturition						
94	Udeh et al. (b)	2019	1041	14	Y (14)	No	N (14)	Y/N/Two samples (14)	Coproparasiotological Direct exam and acetate-acetic acid - formalin sedimentation	N (14)	N	N	N
95	Aninagyei et al.	2020	538	9	Y (9)	No	Diarrhea	Y/Without preservative/One sample (9)	Coproparasitological Formalin-ether sedimentation (+9)	N (9)	N	N	N
96	Bahaa Alaa	2020	100	8	Y (8)	No	Dysentery and Colic	Y/Without preservative/One sample (8)	Coproparasitological Direct exam (8+)	Cyst (8)	N	N	N
97	Barbosa and Pavanelli	2020	42	10	Y (10)	No	N (10)	Y/Without preservative/One sample (10)	Coproparasitological Spontaneous sedimentation and flotation with zinc sulfate (10+)	Cyst (10)	N (10)	N (10)	N (10)
98	Boy et al.	2020	40	2	Y (2)	No	N (2)	Y/With preservative/ Three samples (2)	Coproparasitological Direct exam and ether sedimentation	N (2)	N	N	N
99	Joshi and Scarff	2020	1	1	N	Lungs	Massive pulmonary hemorrhage	Not collected	Cytology in a brochoalveolar lavage specimen	Trophozoite	N	N	N
100	Kumar et al.	2020	1052	1	Y (1)	No	N	Y/Without preservative/N	Coproparasitological Direct exam (+)	Cyst	N	N	N
101	Martviset et al.	2020	1	1	No	Genitourinary tract (1)	Swelling of both lower limbs	Y/With preservative/ Three samples	Coproparasitological Formalin-ethyl acetate sedimentation (-), Urinary sedimentation and permanent staining with Wrigth - Giemsa (+)	Trophozoite	Tetracycline	Y	Recovered
102	Pérez-Hernández et al.	2021 (2020 year to accept)	1	1	Y - appendix (1)	No	Colic	Y/N/N	Coproparasitological N (+), appendix biopsy histopathology (+)	Cyst, biopsy histopathology trophozoite	Surgical and Metronidazole	Y	Recovered
103	Yu et al.	2020	1	1	Y	No	Abdominal pain, Tenesmus and Dysentery	Y/Without preservative/N	Coproparasitological Direct exam and Giemsa stained smear (+)	Trophozoite	Metronidazole	Y	Recovered

[a] Y: Yes; No: Not; N: Not reported; number in parenthesis: person quantity; +: positive for *B. coli*; + and number: quantity person positvity.

associated with the case report published by Walzer et al. (1973). In their article, the authors reported the largest outbreak of human balantidiasis recorded in history, which occurred in Truk Atoll, now called Chuuk Lagoon, in Micronesia. In that outbreak, 110 people were infected through the consumption of water and/or food containing *B. coli* cysts from pigs, which contaminated the local water sources after the passage of a typhoon. The second clinical case report, which most portrayed infections called human balantidiasis, was that of Mccarey in 1952, that is, inserted in the interval between 1932 and 1953. In this article, the infection by *B. coli* was reported in 87 Muslim workers in an Anglo-American company.

With regard to the variable of continent, Asia and South America were the one with the largest number of articles about human balantidiasis, highlighting India in Asia and Brazil in South America. However, Africa, but precisely Ethiopia, was the continent/country in which was retrieved an article with the highest number of people potentially infected by *B. coli*, highlighting in this scenario the epidemiological study by Feleke et al. (2019). In general, the studies carried out and retrieved in the African continent were important in this systematic review, as they updated the epidemiological data on human balantidiasis, since this continent was not identified as relevant in the prevalence of this parasitosis.

Thus, when comparing the total sample of potentially infected individuals, discrepancies can be found between frequencies on different continents, which seem to have confirmed the statistically significant difference. This paradoxical scenario must be examined carefully, since most of the articles retrieved were clinical case reports that involved small sample sizes and occurred in different countries. Conversely, in Asia, the article by McCarey (1952) consisted of a single case report that occurred in Iran, and unlike the other studies, it involved a larger number of infected individuals, i.e., 87 and in the Micronesia/Truk, the United States, that involved 110 infected people in the article written by Walzer et al. (1973). However, when only epidemiological articles were analyzed, without clinical case reports, it was found that the possibility the human balantidiasis can occur again in South America and in Asia. Although of the epidemiological articles on these continents had fewer people potentially infected with *B. coli* than in Africa, the sample panel included in articles from South America and Asia was also smaller, favoring the proportion of the event.

In this systematic review, age information was very difficult to retrieve, since it was absent from most of the articles. Upon associating all articles that reported the participants' age groups, the child was the most infected age group and its sample is mainly reported in epidemiological studies. This age group should be further studied to assess a real susceptibility and sensitivity to infection by the protozoan. However, the adults corresponded to the majority of the sample of infected individuals in clinical case reports. Positivity in adult seems to be related to their greater exposure to sources of contamination by *B. coli*, especially among people that handle livestock, e.g., farmers and/or slaughterhouse workers, which are activities usually carried out by adults.

Several authors have already highlighted different factors as predisposing, i.e., as situations that end up facilitating the invasion of the protozoan *B. coli* into the membrane of the large intestine of humans (Schuster and Ramirez-Ávila, 2008). These factors include concomitant infections by other infectious agents, malnutrition, immunodeficiency, chronic diseases, coprophagic habits due to mental disorders, and alcoholism (Ladas et al., 1989; Moraleda et al., 1980; Esteban et al., 1998; Cermeño et al., 2003; Ferry et al., 2004; Dhawan et al., 2013). Information about comorbidities and/or concomitant infections caused by other biological agents were also retrieved in the articles of this study, mainly in clinical case reports, underscoring the opportunistic nature of this parasite. Although alcoholism has also been identified as a predisposing factor for invasion of the ciliate into the intestinal mucosa, in this systematic review, only six of the retrieved articles reported individuals with alcohol abuse (Bel and Couret, 1910; Ferry et al., 2004; Dhawan et al, 2013; Soleimanpour et al., 2015; Kapur et al., 2016; Kumar et al., 2016). This number of retrieved articles may have failed to represent the real importance of this variable in human balantidiasis. The participants included in the studies may not have reported this addiction out of shame, they may not have been questioned by the health professional and/or researcher, or the author of the article may not have included this information in the article because he considered it irrelevant.

One of the most important elements in the theme of human balantidiasis is physical proximity to pigs, which are the animal species most widely incriminated in the literature as a reservoir of infection (Zaman, 1978). In this systematic review, the physical proximity between humans and pigs proved to be relevant in the transmission of the parasitic disease, in both clinical case reports and epidemiological studies. Therefore, health professionals should always remember to ask patients about their routine, including questions pertaining to proximity to pigs and their excreta, especially in their interactions with farmers, livestock handlers and/or patients with dysentery. However, albeit to a lesser extent, cases were found of potentially infected individuals who stated they were not in proximity to pigs. Nonproximity to pigs is not an exclusion factor for infection, since *B. coli* cysts can contaminate water and food and thus be ingested.

Many individuals included in the articles of this systematic review showed signs of an intestinal infection, i.e., they had gastrointestinal symptoms and/or a positive coproparasitological diagnosis for the evolutionary forms of this parasite. It should be pointed out that the large intestine is considered the organ of choice of *B. coli* (Schuster and Ramirez-Ávila, 2008). Most of the methodologies used in epidemiological studies to detect intestinal infections included a coproparasitological diagnosis. Only the epidemiological study, authored by Khurana et al. (2018), aimed to analyze structures in urinary sediment and Zarbaliyev and Celik (2018) that reported biopsy in appendix.

Reports of extraintestinal forms, albeit few, were also included in the articles analyzed in this review, mostly in clinical case reports. Extraintestinal forms have been identified in a variety of habitats, ranging from the genitourinary tract to lungs, liver, gallbladder, peritoneum, vertebra and eyeballs. However, the extraintestinal infections most frequently reported were in the genitourinary tract and were found mainly in Asian countries (Umesh, 2007; Bandyopadhyay et al., 2013; Karuna and Khadanga, 2014; Khanduri et al., 2014; Soleimanpour et al., 2015; Kaur and Gupta, 2016; Mane et al., 2016; Gupta et al., 2017; Mayuri and Mayuri, 2017; Khurana et al., 2018; Khurana et al., 2019; Martviset et al., 2020). In most of these cases, the patients were women who reported swimming in rivers or streams possibly contaminated with *B. coli*. It is believed that infections of the genitourinary tract by this parasite occur through direct contact of fecal material from the anal region, due to the presence of rectovaginal fistulas or secondary to tissue invasion (Sharma and Harding, 2003). Poloni et al. (2015) pointed out that genitourinary material for the diagnosis of evolutionary forms of *B. coli* should be collected with the utmost care, using sterile collectors in order to avoid contamination of the urine sample with fecal matter, resulting in a false positive diagnosis, a problem that was subsequently reported in India by Gupta et al. (2017).

In general, extraintestinal infections are not commonly expected, given that the parasite does not always invade the mucosa and reach other organs through contiguity, bloodstream and/or lymphatic flow. Among the various sites of extraintestinal infections reported in the articles of this systematic review, one caught our particular attention because it involved the eyeballs. This was described in two case reports, one published in Brazil and the other in India (Pinheiro et al., 2015; Hazarika et al., 2016). In both clinical cases, the patients had blurred vision, wore contact lenses and were diagnosed with the parasite, both in corneal material and in contact lens and their disinfectant solutions. Although the morphology of the protozoan was similar to that of *B. coli*, other ciliate species present in the environment must also be considered as possible infectious agents and/or contaminants in ocular material. In view of this possibility, the 997 individuals with positive diagnosis were identified in this study as potentially infected with *B. coli*.

Still with respect to symptomatology, the majority of infected individuals exhibited symptoms consistent with the infection site, with dysentery being the most frequently reported symptom of invasion of the intestinal mucosa. The higher frequency of symptomatic individuals suggests that the parasite is still poorly adapted to the human organism, triggering symptomatic infections in most cases.

With regard to laboratory diagnostics, specifically coproparasitological diagnosis, it was found that several articles failed to offer important information on this theme. The paucity of information pertaining to methodology may render its reproducibility in other studies unfeasible. Most of the articles that included this information stated that stool samples were collected without chemical preservative, particularly in the case of clinical case reports. This type of collection is usually performed when the stool sample is subjected to direct examination, a technique that was the most widely reported in the articles retrieved for this meta-analysis. In *B. coli* research, direct examination has been the most recommended technique for the diagnosis of the evolutionary forms of this parasite, mainly in research of trophozoites (Barbosa et al., 2016). In the case of humans, the use of this technique on fresh stool samples without chemical preservatives is even more relevant since, according to Woody and Woody (1960), Areán and Koppisch (1956) and Baskerville et al. (1970), trophozoite forms usually correspond to about 80% of those eliminated in feces from infected humans. These statements are in line with the findings of this review, given that this evolutionary form was the one most frequently reported in the studies that included coproparasitological diagnosis.

A slightly different situation was revealed in epidemiological studies, which may have opted to use chemical preservatives because of the number of stool samples collected and to facilitate their transport. However, depending on the chemical solution used, it may not have been suitable to preserve the evolutionary form of the trophozoite, thus leading to a false negative diagnosis. In other words, the number of cases of infected individuals reported in these studies could have been even higher if fecal samples had been collected without preservative chemical. This situation was described in the epidemiological articles by Udeh et al. (2008), Boonjaraspinyo (2013), Biolchi et al. (2015), Feleke (2015), Sandoval et al. (2015), Alomashi and Al-Shabbani (2019), Feleke et al. (2019) and Boy et al. (2020), who reported having used chemical as a preservative of stool samples.

In addition to direct examination, coproparasitological sedimentation techniques have also been widely reported in the articles retrieved for this review. According to Barbosa et al. (2016), similar techniques have already been recommended for the study of cysts of this protozoan in the feces of other host species, possibly because of their dense parasitic structures. The collection of multiple samples on different days is generally indicated for the diagnosis of *B. coli* cysts, since these evolutionary forms are released intermittently in the host's feces (Solaymani-Mohammadi and Petri, 2006). However, most of the articles in this review that reported the diagnosis of *B. coli* cysts did not report the number of stool samples collected.

In general, the articles examined this systematic review revealed a predominance in the diagnosis of the trophozoite form of *B. coli* in different human samples, including stool and other biological materials, which were typically collected in the case of extraintestinal infections. However, to ensure diagnostic reliability, a more specific technique is required to identify ciliated trophozoites in biological samples, such as molecular biology techniques, since the phylum Ciliophora comprises several genera and species (Lynn, 2008). Whenever a ciliated trophozoite is detected in a human biological sample by means of optical microscopy, it has immediately been associated with the species *B. coli*, as if there was only this specie of ciliated protozoan.

The articles consulted in this review indicated that the combined use of the drugs tetracycline and metronidazole has increased, starting from the outbreak of human balantidiasis in Truk Atoll. Although no study to date has evaluated the effectiveness of this drug combination, these drugs are still the most suitable ones for the treatment of human balantidiasis (Medical Letter, 2004). Although few cases of death were reported in these articles, it is known that the acute form of balantidiasis can lead to fulminant conditions, i.e., death occurs within about a week (Schuster and Ramirez-Ávila, 2008). This emphasizes the importance of making an adequate and rapid diagnosis in order to provide a more specific treatment, and always including a test of cure. Surprisingly, this variable was widely reported in the retrieved articles, especially in the case reports.

In our extraction of pertinent information for this systematic review, we found that many articles did not provide detailed data. This made it very difficult to perform the important statistical analyses involved in a meta-analysis, which generally includes the odds ratio. This statistical data may be published directly in the epidemiological article itself or calculated by the authors of the systematic review based on the data provided in the article. Unfortunately, in our review of articles on human balantidiasis, we were unable to perform this type of analysis due to the insufficiency of the information published, the small number of articles on epidemiological studies and mainly due to the high heterogeneity evidenced in the general index and in the analysis by year and continents. Therefore, a meta-analysis of proportions was produced using information that is generally available, such as the year and continent of publication.

This review clearly evidenced the paucity of articles retrieved on the theme of human balantidiasis. Classic articles could not be retrieved, such as that by Covée and Rijpstra (1961), who reported one of the highest frequencies of infection by *B. coli* (28%) in Papua New Guinea, and even less so regional papers such as that by Machado et al. (1969), who reported the frequency of balantidiasis in 0.7% of patients treated in the city of Niterói, Rio de Janeiro, Brazil. This fact underscores the limitation of systematic reviews, especially when it comes to highly neglected parasitic diseases such as infection by *B. coli* or even by other ciliates that may also infect humans but that are traditionally classified simply as *B. coli* when detected in human biological samples.

CRediT authorship contribution statement

Rayana Katylin Mendes da Silva: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Laís Verdan Dib:** Methodology, Investigation, Writing – review & editing. **Maria Regina Amendoeira:** Methodology, Data curation, Writing – original draft, Writing – review & editing. **Camila Carvalho Class:** Methodology, Investigation, Writing – review & editing. **Jessica Lima Pinheiro:** Methodology, Investigation, Writing – review & editing. **Ana Beatriz Monteiro Fonseca:** Methodology, Data curation, Writing – original draft, Writing – review & editing. **Alynne da Silva Barbosa:** Conceptualization, Supervision, Methodology, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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