Seroprevalence of *Toxoplasma gondii* in children: A systematic review and meta-analysis

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Abstract: *Toxoplasma* infection during childhood may cause severe effects for children and their offspring. Here, we initiated a systematic review to estimate the global prevalence of toxoplasmosis. All databases were searched for publications published between January 2000 and March 2021, including studies on the prevalence of *Toxoplasma gondii* in children (1 day-15 years). The overall prevalence rate of toxoplasmosis was evaluated with a 95% CI in global and WHO regions. Toxoplasmosis prevalence and the population size were analysed using linear regression to arrive at this conclusion. As a result, 63 articles included 29342 children from 18 countries in the systematic analysis. The total prevalence rate of toxoplasmosis in children was 0.2% (95% CI: 0.195 - 0.204%). The African region had the highest prevalence rate of 0.28% (95% CI: 0.5-0.55%), while the South American and US regions had the lowest at 0.166% (95% CI: 0.01-0.33%). The prevalence rate among children is very high. Further examination and investigation of the parasite among children is required to reduce the occurrence of new infections or prevent complications of the disease.

Keywords: *Toxoplasma gondii*; Seroprevalence; Children; Meta- analysis; Systematic review

1. Introduction

Toxoplasmosis is an infectious disease that results from infection with an obligate intracellular parasite called *Toxoplasma gondii*. Usually, this infection results from handling soil, water, and foods contaminated with Oocytes or by consuming raw or undercooked meat that contains tissue cysts (Bradyzoite) [1]. Usually, toxoplasmosis is diagnosed by serological tests that detect the presence of the parasite antibodies or by direct observation of the parasite in stained tissues and other biopsies [2]. The parasite can also be isolated from blood or other body fluids such as the cerebrospinal fluid, for example (CSF)[3]. Molecular techniques can be used to detect the parasite DNA in the amniotic fluid. As for severe cases, an MRI can be used [4].

In healthy people that are infected with *toxoplasma* infection, symptoms often do not appear due to the ability of their immune systems to prevent the parasite from causing the disease [5]. If any symptoms appear, they are mild and similar to influenza-like symptoms [6]. As in infants born to infected

mothers, they may suffer from hearing loss, enlarged liver and spleen, yellowing of the skin, mental disability, and blindness [7]. In immunosuppressed or immuno−compromised people, toxoplasmosis may cause many serious complications, such as seizures, lung problems, and encephalitis [8].

Many factors, such as the geographical location and the population's socioeconomic status, affect the distribution and spread of toxoplasmosis among different regions of the world [9]. The spread rate of Toxoplasma may decrease in highly cultured communities. Conversely, the rate of infection among people in low-cultured communities increases [4]. Some reports indicated that infection rates among the USA population were 11.14% [10], Italy 21.4% [11], Iran 45.12% [12], in the State of Amazonas, Brazil, it was 56.7% [13], and in rural Malaysia, it was 69.9% [14].

If compared with studies that reviewed infection among the population, especially women, there are very few studies of toxoplasmosis in children. Many studies have been limited to referring to infection rates among newborns born from infected mothers, alluding to the parasite's transfer from the mother to the foetus and then to the baby via the placenta. In a study conducted in China, many studies have been limited to referring to infection rates among newborns born from infected mothers, alluding to the parasite's transfer from the mother to the foetus and then to the baby via the placenta. The infection rate among children was 0.04%, 25%, 17.44%, 58.5%, 16.6%, and 19.35% for China[15], Iraq[16], Turkey [17], Ghana [18], Saudi Arabia [19], and Pakistan [20], respectively.

Toxoplasmosis infections among children are no less important than in adults. Therefore, attention to the general health of this group and conducting periodic examinations to confirm their safety from diseases is a priority that must be taken into account. Despite the lack of studies on children's infections, this paper aimed to provide an idea of the extent of seroprevalence of toxoplasmosis in the form of a systematic review.

2. Methods

2.1 Search strategy

To search for articles that dealt with toxoplasma prevalence among children from the beginning of 2000 to March 2021, the following keywords were used to search for articles that dealt with toxoplasma prevalence among children from the beginning of 2000 to March 2021: *Toxoplasma gondii*, prevalence, epidemiology, seroprevalence, incidence, and children. The following databases: Pubmed/line, science direct, Google Scholar, Scileo, DOAJ, Springer, and Hindawi, in addition to other local databases, were searched. Articles in different languages were involved.

2.2 Data filtration

After collecting 143 studies from different countries and geographical regions, we excluded 43 studies because they included prevalence of

t*oxoplasmosis* and other parasites, 11 studies because they were review articles in origin, and 26 studies because they were duplicated. Review articles studies were included (Fig.1).

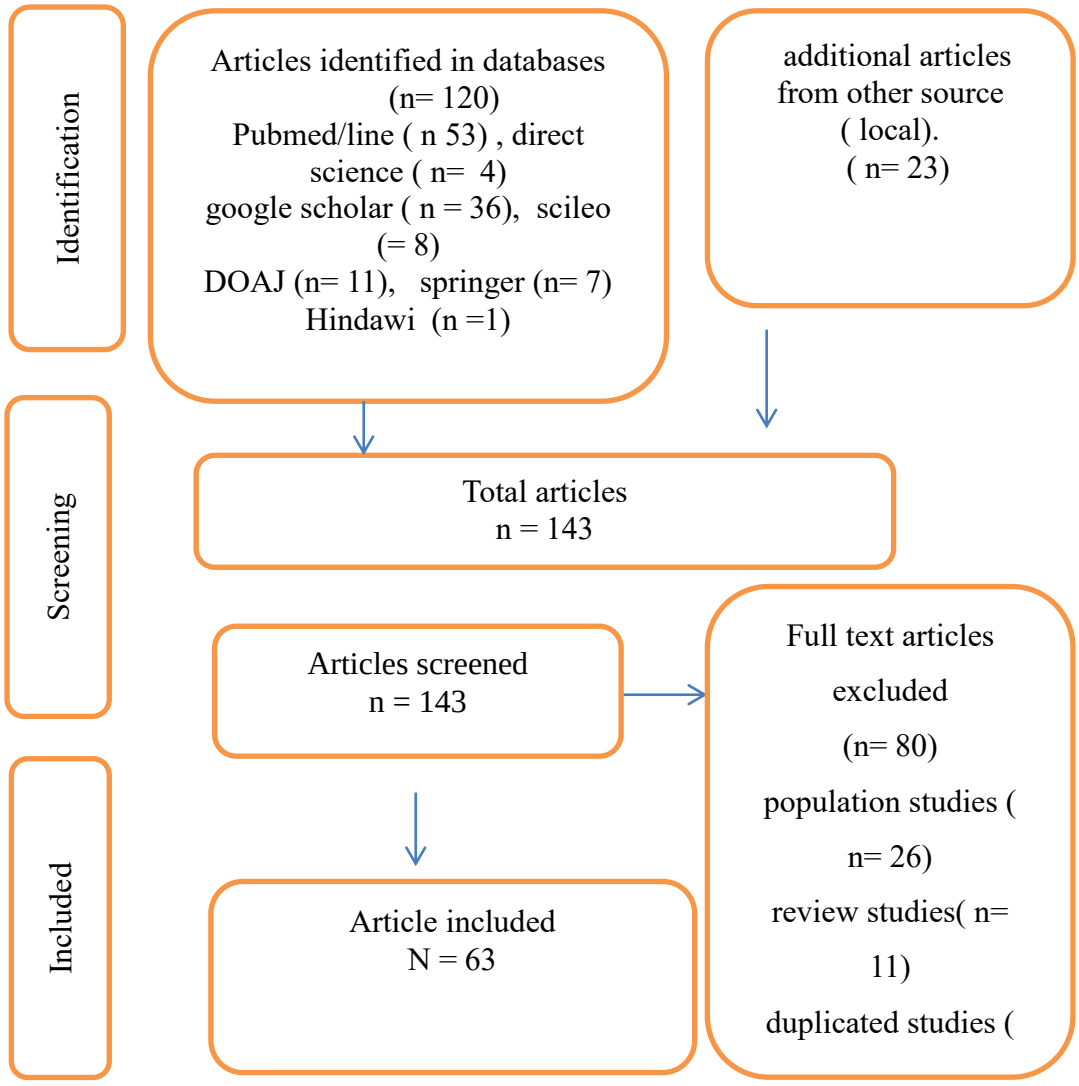

Fig (1): Flow chart of articles and study strategy.

2.3 Data extraction

From 63 studies, the following data were extracted: the names of the authors; the country; the province, the year; the method of diagnosis; the total number of people tested; the total infected people; the sex; age of the infected patients; and the relationship of the infected rate with some risk factors.

2.4 Statistical methods

SPSS 24, (IBM,USA), was used to determine correlation values and linear regression analysis (Fig. 2). Also, to extract the prevalence ratio, weighted population prevalence, *P.* value and confidence interval (CI) of all studies, we used the comprehensive meta-analysis program v3 (Biostat, Inc., USA)[21] .

3. Results

From 18 countries, 63 datasets examined eligibility. The total number of children examined was 29342. The number of *T. gondii* infections was 5857. The incidence rate was 0.2% (95% CI: 0.195-0.204). The prevalence rate ranged between 0.029% in healthy Turkish children and 0.966% in Egyptian children with autism (Table 1; Fig. 3). The correlation rate between the overall number and the number of children infected was 0.806. The meta-regression analysis showed a highly significant correlation between the parasite infection and the increase in the overall number (Fig. 2).

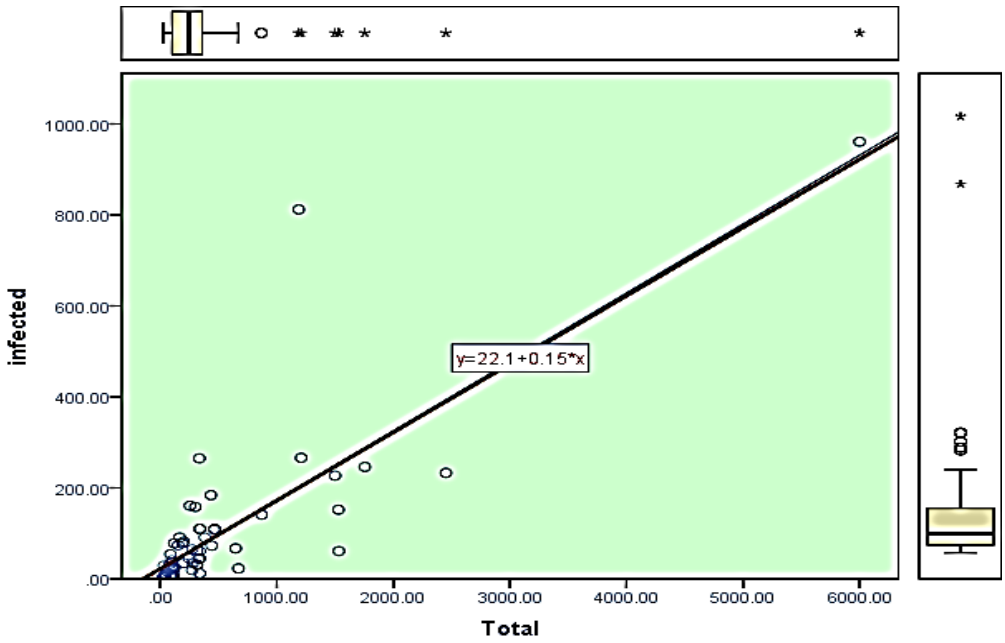

Fig (2): liner regression between total examined and infected children.

3.1 *Toxoplasma* prevalence according to geographical areas

The highest prevalence of *T. gondii* was in Africa at 0.28% when it infected 800/2833 (95% CI: 0.5 0.55), while the lowest prevalence was 0.166% in South America and the USA where just 830/4995 (95% CI: 0.01-0.33) were infected. In Asia, the incidence rate was 0.192%, and the number of infections was 3937/20491 (95% CI: 0.12-0.3). In Europe, the infection rate was 0.25%; the number of children affected was 290/1144 (95% CI; 0.01- 0.52) (Tab. 2).

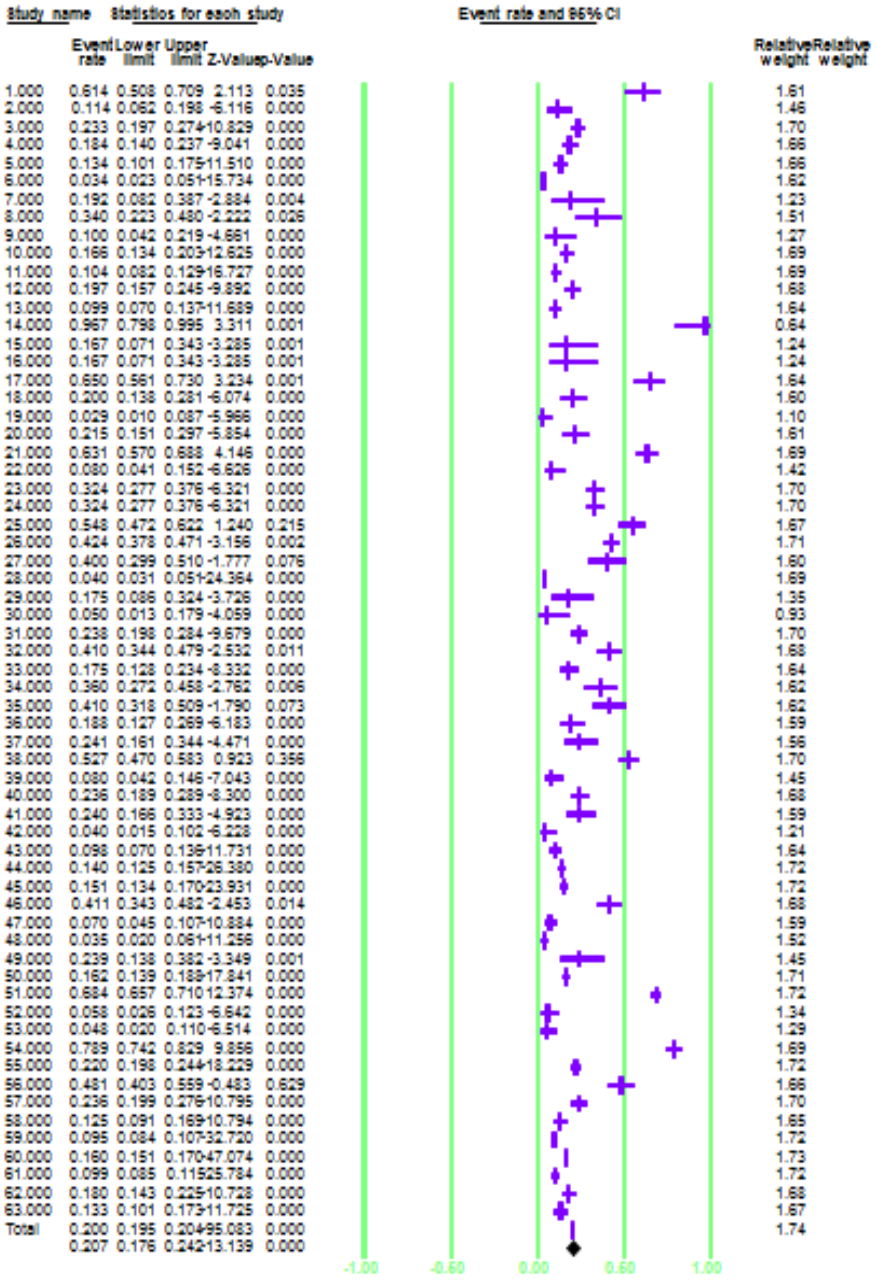

Fig (3): Forest plot of the global prevalence of *T. gondii* in children.

Table 1: Global seroprevalence of T. gondii as 63 databases.

Ref. number	Country	Infected/ total	Rate	95% CI	*P*.value
[22]	Iraq	45/88	0.61	0.5 -0.7	0.035
	Iraq	10/88	0.11	0.06-0.198	0.00
[23]	Iraq	108/463	0.233	0.196- 0.273	0.00
[24]	Serbia	45/245	0.183	0.14 - 0.237	0.00

[25]	Saudia	44/328	0.134	0.101 - 0.175	0.00
[26]	Iran	23/671	0.034	2.288 - 5.105	0.00
[27]	Maxico	5/26	0.192	0.082 - 0.387	0.004
[28]	Iran	17/50	0.34	0.22 - 0.48	0.026
	Iran	5/50	0.1	0.042 – 0.219	0.003
[29]	Romania	73/441	0.165	0.133 - 0.203	0.00
[30]	Mali	67/647	0.103	0.082 - 0.129	0.00
[31]	Chine	62/314	0.197	0.157 - 0.245	0.00
	Chine	31/314	0.099	0.07 – 0.136	0.00
[32]	Egypt	29/30	0.966	0.79 - 0.995	0.00
	Egypt	5/30	0.166	0.071 – 0.343	0.00
	Egypt	5/30	0.166	0.071 – 0.343	0.00
[33]	Egypt	78/120	0.65	0.56 - 0.729	0.00
	Egypt	24/120	0.2	0.137 - 0.281	0.00
[34]	Turkey	3/102	0.029	0.01 – 0.87	0.00
[35]	São Tomé	26/121	0.214	0.15 - 0.296	0.00
[36]	São Tomé	161/255	0.631	0.57 - 0.688	0.00
[37]	Brazil	8/100	0.08	0.04 – 0.15	0.00
[38]	Brazil	110/339	0.324	0.276 - 0.376	0.00
	Brazil	110/339	0.324	0.276 - 0.376	0.00
[39]	Island	91/166	0.54	0.47 - 0.622	0.215
[40]	Brazil	184/434	0.423	0.378 - 0.47	0.00
[41]	Colombia	32/80	0.4	0.298 - 0.51	0.07
[42]	Colombia	61/1533	0.04	0.031 – 0.051	0.00
[43]	Egypt	7/40	0.175	0.086 – 0.324	0.00
	Egypt	2/40	0.05	0.012 – 0.479	0.00
[44]	Nigeria	91/382	0.238	0.198 - 0.283	0.00
[45]	Egypt	82/200	0.41	0.343 - 0.479	0.01

	Egypt	35/200	0.175	0.128 - 0.234	0.00
[46]	Iraq	36/100	0.36	0.272 -0.458	0.006
	Iraq	41/100	0.41	0.318 - 0.508	0.07
[47]	Iran	22/117	0.188	0.127 - 0.269	0.00
	Iran	20/83	0.24	0.161 - 0.344	0.00
[48]	Nigeria	158/300	0.526	0.47- 0.58	0.35
[49]	Brazil	9/113	0.08	0.041 – 0.146	0.00
[50]	Brazil	65/276	0.235	0.189 - 0.289	0.00
[51]	Iraq	24/100	0.239	0.166 - 0.333	0.00
	Iraq	4/100	0.04	0.015 – 0.105	0.00
[52]	Iran	31/316	0.098	0.069 - 0.136	0.00
[53]	USA	246/1755	0.14	0.124 - 0.157	0.00
[45]	China	227/1500	0.151	0.134 - 0.17	0.00
[55]	Poland	78/190	0.41	0.342 - 0.481	0.014
[56]	Nigeria	19/272	0.069	0.045 – 0.106	0.00
[57]	Iran	12/340	0.035	0.02 – 0.061	0.00
[58]	Egypt	11/46	0.239	0.137 - 0.382	0.001
[59]	Iran	141/869	0.162	0.139 - 0.188	0.00
[60]	Iran	812/1187	0.684	0.657 - 0.709	0.00
[61]	Iran	6/104	0.058	0.026 – 0. 11	0.00
	Iran	5/104	0.048	0.02 – 0. 11	0.00
[62]	Iran	265/336	0.788	0.741 - 0.829	0.00
[63]	Iran	266/1209	0.22	0.197 - 0.244	0.00
[64]	Iraq	74/154	0.48	0.402 - 0.559	0.628
[65]	Myanmar	110/467	0.235	0.199 - 0.276	0.00
[66]	China	35/281	0.124	0.09 - 0.168	0.00
[67]	China	233/2451	0.095	0.084 – 0.107	0.00
[68]	China	961/6000	0.16	0.151 - 0.169	0.00

[69]	Iran	152/1529	0.099	0.085 – 0.115	0.00
[70]	Chine	61/339	0.179	0.142 - 0.224	0.00
	Chine	45/339	0.132	0.100 - 0.173	0.00
		5857/29342	0.2	0.195 - 0.204	0.00

Table 2: prevalence of *T. gondii* as subgroups

Parameters		Number of data Sets	Infected/ total	Rate	95% CI
South America and USA		**10**	**830/4995**	**0.166**	**0.01 – 0.33**
Brazil		6	486/ 1601	0.30	0.17 – 0.43
Colombia		2	93/1613	0.057	0.0 -0.1
Mexico		1	5/26	0.192	0.082 - 0.387
USA		1	246/1755	0.14	0.124 - 0.157
Asia		**32**	**3937/20491**	**0.192**	**0.12 – 0.3**
China		8	1655/ 11538	0.143	0.11- 0.2
Myanmar		1	110/467	0.235	0.199 - 0.276
Iran		14	1777\6965	0.255	0.09 – 0.36
Iraq		8	351/1193	0.294	0.11 – 0.44
Saudi		1	44/328	0.134	0.101 - 0.175
Africa		**16**	**800/ 2833**	**0.28**	**0.5 0.55**
Mali		1	/647	0.103	0.082 - 0.129
Egypt		10	278/856	0.32	0.12 – 0.53
São Tomé		2	187/ 376	0.49	0.22 – 0. 53
Nigeria		3	268/ 954	0.28	0.03 – 0.84
Europe		**5**	**290/ 1144**	**0.25**	**0.01 – 0.52**
Poland		1	78/190	0.41	0.342 - 0.481
Romania		1	73/441	0.165	0.133 - 0.203
Turkey		1	3/102	0.029	0.01 – 0.87
Serbia		1	45/245	0.183	0.14 - 0.237
Island		1	91\166	0.54	0.47 - 0.622
Study year	2002	1	4/434	0.423	0.378 - 0.47
	2006 - 2009	10	1560/4448	0.35	0.13 – 0.46
	2010 - 2013	8	727/4428	0.16	0.06 – 0.44
	2014 - 2017	13	23/11007	0.17	0.12 – 0.32
	2018 - 2021	31	1563/ 9146	0.17	0.16 – 0.31
Test methods	ELISA	47	3701/24320	0.15	0.15 – 0.24
	IFAT	9	1637/3305	0.49	0.16 – 0.53
	LATEX	5	378/916	0.41	0.05 – 0.63
	Agglutination	1	67/647	0.10	0.402 - 0.559
	VIDAS	1	74/154	0.48	0.082 - 0.129

3.2 *Toxoplasma* prevalence as years

Although the review aimed to examine the prevalence of *T. gondii* among children for the period from 2000 to 2021, it did not record the presence of any datasets documenting the parasite infection during the years 2000 and 20001. In addition, the

review did not record the existence of research during the years 2003-2005.

The incidence rate in 2002 was 0.423% (95% CI: 0.378-0.47) when the total number of children affected was 184/434 from only one dataset. It was the highest rate in the years. The lowest incidence rate of 0.17% was recorded in the years 2014-2017 (95% CI: 0.12-0.32) and in the years 2018-2021 (95% CI: 0.16-0.31), with the highest number of datasets (31). In 2006-2009, the incidence rate was 0.35% (95% CI: 0.13-0.46), and in 2010-2013, it was 0.16% (95% CI: 0.13-0.46) (Table 2).

3.3 Toxoplasma prevalence as diagnosis method

The ELISA method is used in most articles, where the method was used in 47 datasets repeatedly. The incidence rate according to this method was 0.15% (95% CI: 0.15-0.24) despite that. (Agglutination and VIDAS) were infrequently used diagnostic methods. Since you reported below results of 0.10% (95% CI: 0.402-0.559) and 0.48% (95% CI: 0.082-0.129), that means it was repeated two times, not one time. IFAT was repeated in nine datasets and averaged 0.49% (95% CI: 0.16-0.53).

3.4 Risk factors of *T. gondii*

Not all 63 datasets included the association of *T. gondii* infection in the risk factors. Only 24 studies were interested in them. In addition, no single study mentioned all the risk factors.

This review showed that the chronic infection rate is the highest, as the IgG antibody was at a rate of 0.19% (95% CI: 0.17-0.26), the IgM antibody and IgG were presented together at a rate of 0.018% (95% CI: 0.01-0.03), while the acute infection and IgM were presented at a rate of 0.036% (95% CI: 0.03-0.09). It should be mentioned that from 63 datasets, IGM concentrations were measured in 39, IgG in 59, and IgM + IgG in 16 datasets (Table. 3).

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Parasite prevalence rates in rural residents were 0.16% (95% CI: 0.07-0.38), and urban residents had a lower prevalence of toxoplasmosis 0.135% (95% CI: 0.08 - 0.28). These results were accompanied bypresence of cats in the homes of (393) of those infected with toxoplasmosis, with a rate of 0.274% (95% CI: 0.05-0.42), while 313 infected with the parasite did not possess any cats, and the infection rates among them were 0.146% (95% CI: 0.01-0.3). The number of infected people who contacted cats or who interacted with them was 618/3668, a percentage of 16.84 % (95% CI: 0.12-

0.34). This was higher than the infection percentage for those who did not deal with cats, 0.12% (95% CI: 0.04-0.24), where the total number was 647/5620 (Table. 3).

Dealing with contaminated soil was the cause of infection of 511/3125, with a rate of 16% (95% CI: 0.09-0.28). Children that drank water from wells and rivers were infected at a 17% (95% CI: 0.05–0.38) rate. The overall infection rate was 426/2476. 126/919 infected children consumed fresh vegetables and fruits; the infection rate was 13% (95% CI: 0.08-0.17); while eating raw meat was the cause of transmitting the infection to 240/1249 of the children, 19.2% (95% CI: 0.07-0.48). Public health is an important aspect of infection prevention. Maintaining health is an important reason for hand washing. The review indicated that 416/2456 children who do not care about public hygiene were infected at 17% (95% CI: 0.03-0.3) (Table.3).

It is self-evident to say that the Toxoplasma parasite, like other pathogens, takes advantage of the weak immune system of the host, thus infecting a person with some diseases may facilitate the task of the parasite to spread and cause disease. In 60/350 of the children infected with autism, the presence of toxoplasma was found at a rate of 17(95% CI: 0.05–0.33), while 23/671 of the children infected with HIV were also infected with the parasite at a rate of 3.4% (95% CI: 0.028–0.05). Various cancers and what caused a waste of the patient's energy were the causes of infection for 62/314 with lymphoma, 19.7% (95% CI: 0.157-0.245), while 61/339 of the children that were infected with leukemia had 18% (95% CI: 0.142-0.224). Toxoplasmosis was linked to 836/3035 children with neurological disorders, accounting for 27.5% (95% CI: 0.04-0.89). The relationship between parasite infection and congenital deformities of newborns is explained by having 45/88 (51.13%) suffering from congenital deformities (95% CI: 0.5-0.7). Of 36/100 children affected by thalassemia major, 36% (95% CI: 0.272-0.458) were reported. As for the rest of the diseases, 59/381 were infected with the Toxoplasma parasite at 15.4% (95% CI: 0.14–0.23) (Table.3).

Table 3: Risk factor of global Toxoplasmosis infections.

Parameters		Total/ infected	Rate	95% CI
Antibodies	IgM	713/19763	0.036	0.03 – 0.09
	IgG	5226/ 27477	0.19	0.17 – 0.26
	IgG + IgM	244/12359	0.018	0.01 – 0.03
Gender	Male	2610/ 13065	0.199	0.17 – 0.29
	Female	2552/ 12380	0.2	0.17 – 0.31
Age	1-11 months	148/2182	0.067	0.03 – 0.44
	1-5 years	575/3619	0.16	0.13 – 29
	6-10 years	2784/15972	0.174	0.17 – 0.29
	11-15 years	1334/5939	0.224	0.2 – 0.34
Residential	Urban	544 / 4035	0.135	0.08 – 0.28

	Rural	584/3630	0.16	0.07 – 0.38
Have a cat at home?	Yes	393 / 1433	0.274	0.05 – 0.42
	No	313 / 2132	0.146	0.01 – 0.3
Contact with cats	Yes	618/ 3668	0.17	0.12 – 0.34
	No	647/ 5620	0.12	0.04 – 0.24
Contact with soil	Yes	511/ 3125	0.16	0.09 – 0.28
	No	572/ 3785	0.15	0.03 – 0.3
Water source	Tap	344/ 2048	0.16	0.09 – 0.38
	Well & others	426/ 2476	0.17	0.05 – 0.38
Wash hand	No	416/ 2456	0.17	0.03 – 0.3
	Yes	250/ 2704	0.12	0.01 – 0.49
Consumption raw fruit & vegetable	Yes	126/ 919	0.13	0.08 – 0.17
	No	117/ 942	0.12	0.05 – 0.19
Consumption meat	Yes	240/ 1249	0.19	0.07 – 0.48
	No	441/ 2443	0.18	0.05 – 0.17
Correlation with other diseases or disorders	Autism	60/ 350	0.17	0.05 – 0.33
	HIV	23/671	0.034	0.028 - 0.05
	Lymphoma	62/314	0.197	0.157 - 0.245
	Leukemia	61/339	0.018	0.142 - 0.224
	Neurological disorder	836/3035	0.275	0.04 – 0.89
	Congenital deformities	45/88	0.61	0.5 -0.7
	β-Thalassemia Major	36/100	0.36	0.272 -0.458
	Different diseases	59/381	0.15	0.14 – 0.23

4. Discussion

The presence of just 63 studies during 20 years concerned with toxoplasmosis among children (at the rate of 3 articles per year) is an indication of the lack of interest in this category of the population. With the presence of 2.2 billion children (between 1 and 14 years old) in the world, 2 billion of them live in developing countries. Therefore, our systematic review is the first global study of its kind that focuses on infecting children with *T. gondii* [71].

The high infection rate among children (80%) is a wake-up call to the great danger the parasite infestation causes among children. The infection of 20% of children in the world with toxoplasmosis is much greater than the infection of 1.1% of pregnant women [72]. The prevalence rate among children in Mexico was 0.616% [73]. In Greece, 8.1% in the year (2004) alone [74]. In America, 0.91% of children aged 6–11 years were infected [10], and in the United Arab Emirates, 12.5% [75].

Factors such as culture or education [76], geographical location, and climate [77] have a significant impact on the spread of diseases, including toxoplasma [78]. These facts can be reflected in the results of our analysis, as Africa has the highest prevalence rates, while Latin America and the United States have the lowest. This result is consistent with what was confirmed by a WHO-supported study [79]. High childhood infections are, in

some cases, the result of mothers infected with the parasite [80].

Despite the increase in studies in recent years compared to previous years and the increasing number of children undergoing toxoplasma detection, our current review showed a decline in the parasite prevalence rate. The prevalence was the highest in 2002, but reached the lowest rate in 2018-2019. These results coincide with concern for public health, increased health education, and an interest in health care and early screening [78]. There are numerous methods for detecting Toxoplasma [71,79]. The ELISA method is the best serological diagnostic method as it combines speed, ease of implementation, and accuracy of results [81]. It is also possible to compare acute and chronic infections by detecting the presence of parasite-specific antibodies [82]. In this analysis, we noticed a high incidence of IgG, which means the presence of chronic infections that are caused by previous (may be cured) or asymptomatic infections [83]. The difference in gender infection is very small, which may be due to small numbers or differences in study areas and diagnostic methods, sometimes the way that samples are selected. Other research suggests a higher male incidence rate [84]. The nature of work performed by both males and females (particularly in developing countries) and changes in hormone concentrations may be the primary reasons for the variation in gender infections [85]. Consequently, these differences were not noticed in younger age groups. The prevalence rate increased with increasing age, which is interesting (although not new). The majority of these children's infections were caused by infected mothers [72]. The increase in infection rate in older age groups is due to many reasons, such as feeding methods, starting to move, playing, connecting with animals, and even working [86].

The nature of the rural environment, the presence of polluted soil, the handling and possession of various animals; all these factors contribute to the increased prevalence rate in rural areas than in urban [87]. The results of this analysis are coordinated with many studies that confirm the increase in infection rates with the consumption of fresh vegetables and fruits [88], fresh meat, and contaminated water [89].

Toxoplasma is an opportunistic parasite, which exploits the weakened immune system to attack the host's cells [90]. For this reason, infections are more frequent and severe among immune-compromised people [91]. These parasites attack nerve cells and cause various impairments and neurological and behavioural disorders by following various mechanisms [92]. autism spectrum disorder is a neurobehavioral disorder [93] that increases the risk of being exposed to contaminants that induce disease transmission, including toxoplasma. On the other hand, toxoplasma and the resulting increased secretion of many neurogenic hormones exacerbate autism [94]. Blood transfusion is one of the common methods of *toxoplasma* transmission [95], so infection with the

parasite is associated with blood diseases such as thalassemia [96] and blood cancers [97].

5. Conclusion

The systematic review indicated a high prevalence of the parasite among children (especially newborns), which means that there are high infections among women of childbearing age. The modest size of the study is due to the short number of research publications, and this necessitates additional work in this field, as well as specialist research personnel in childhood infections.

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