International Journal of
Health Sciences
(IJHS)

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CARI Journals

International Journal of Health Sciences

ISSN: 2710-2564 (Online)

Vol. 7, Issue No.8, pp. 1 - 18, 2024

www.carijournals

Toxoplasmosis in Public Health: Risks, Diagnosis and Therapeutic

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Accepted: 30th Oct, 2024, Received in Revised Form: 14th Nov, 2024, Published: 22nd Nov, 2024

Abstract

Purpose: Based on the notoriety of the prevalence of the disease in the current context, this paper aims to cite the main forms of treatment currently applied, highlighting the particularities of each medication used, in addition to highlighting the future perspectives in relation to the disease and preventive measures.

Methodology: To produce the article, a literature review was carried out based on books, epidemiological and experimental papers through searches in Google, academic databases and PubMed.

Findings: Recent studies show a possible relationship between toxoplasmosis and other diseases of the Central Nervous System, such as Parkinson's. Despite years of research aimed at producing an effective vaccine against the disease, it has not yet been possible to obtain one, although there is progress.

Unique Contribution to Theory, Policy and Practice: By reviewing data already present in the literature, it is possible to better clarify which are the best forms of diagnosis, as well as the development of new treatments. The graphical analysis of the results indicated fewer studies about risk factors and prevention methods, showing a lack of discussion about these topics and a need to spread this information to try to lower the prevalence of the disease. Therefore, the evolution of disease diagnosis techniques helps in the beginning of treatment, preventing the worsening of the condition in more susceptible people.

Keywords: *Toxoplasmosis, Toxoplasma gondii, Clinical aspects, Parasitic infection.*

1) INTRODUCTION:

Toxoplasma gondii is an obligate intracellular protozoan that causes toxoplasmosis, a disease of medical and veterinary importance. The transmission of toxoplasmosis occurs mainly through the oral and congenital routes, where the disease is transmitted from mother to fetus (Dubey and Beattie, 1998; Attias *et al.*, 2020). There are also other forms of transmission of the disease, such as blood transfusion and organ donation, although less frequent (Dubey and Beattie, 1998; Guimarães *et al,* 2014). In general, immunocompetent people do not have symptoms of the disease, but people who have acquired toxoplasmosis vertically (congenitally) or who are immunosuppressed have more severe symptoms of the disease, such as neurological disorders involving mental confusion and seizures, lymphadenopathy, hepatosplenomegaly, chorioretinitis and intracranial calcifications (Bahia *et al*., 1992, Howe, Summers and Sibley, 1996; Zhang *et al*., 2019; Sponchiado and Da Silva, 2023).

The main route of transmission of toxoplasmosis occurs horizontally, that is, by ingesting water or food contaminated by the parasite *Toxoplasma gondii*. The cycle begins with the ingestion of cysts (containing bradyzoites) or oocysts (containing sporozoites), followed by the release of parasitic forms into the host's body (Dubey *et al*., 1986; Attias *et al*., 2020). In the intermediate host, man or any other animal, the released bradyzoites and sporozoites differentiate into tachyzoites and invade the cells, initiating the process of replication by endodiogeny, where daughter cells are generated within the mother cell (Souza, 1974; Attias *et al*., 2020). Later, tachyzoites dedifferentiate into bradyzoites, forming tissue cysts (Frenkel, 1973; Barbosa *et al*., 2014; Sanchez et al., 2023). In the definitive host, felines, bradyzoites differentiate into tachyzoites (which invade new cells to multiply) and gametocytes, which are divided into microgametes (male gametes) and microgametes (female gametes). These gametes fuse and mature in the oocyst, and are later released in the feces of the feline, starting the cycle again (Frenkel *et al*., 1970; Souza, 1974; Esteves, 2022).

The formation of cysts classifies the chronicity of the disease, which can be reactivated depending on the immunological condition of the host and environmental factors favorable to the protozoan (Lyons *et al*., 2002; Daher *et al*., 2021). For this reason, toxoplasmosis may also be associated with the emergence of other diseases, mainly associated with the central nervous system (Minto and Roberts, 1959; Buitrago *et al*., 2024).

2) METHODOLOGY:

A literature review was carried out based on books, epidemiological and experimental articles with the objective of gathering information about the protozoan *Toxoplasma gondii.* The terms searched were: "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis symptoms", "toxoplasmosis diagnosis", "toxoplasmosis treatment", "toxoplasmosis prevention", "toxoplasmosis risk factors", "toxoplasmosis vaccine" by searching Google Scholar and PubMed databases. The selected articles were published between 1908 and

2024. The approach is quantitative-qualitative of the descriptive type involving *Toxoplasma gondii.*

3) RESULTS:

3.1) PREVENTION

The prevention of toxoplasmosis involves simple measures that are related to washing food, cooking and freezing the meat to be consumed, washing hands after handling raw meats and after contact with cats. In addition, the control of rats and insects through the correct disposal of garbage and animal waste, boiling of untreated water for consumption and the washing of fruits, vegetables and legumes contribute to reducing the risk of infection by *T. gondii* (Brazil, 2009). A study by Branco *et al.* (2012) also reveals the importance of training health professionals in relation to the knowledge of toxoplasmosis and its etiological agent, since, in the study in question, most professionals were unable to answer which evolutionary forms of *T. gondii* are capable of infecting humans. In addition, they also conclude that the correct interpretation of serological tests helps in the prevention and treatment of congenital toxoplasmosis, which was the focus of the study.

3.2) DIAGNOSIS

Clinical diagnosis presents some challenges, because for most people, the disease presents asymptomatically or with nonspecific symptoms. In the case of laboratory diagnosis, direct or indirect methods are used, as already mentioned. When congenital toxoplasmosis is identified or in immunosuppressed patients, the investigation should extend to imaging tests, since the formation of brain and eye cysts can occur, which can lead to blindness. Considering that about 80% of newborns congenitally infected with toxoplasmosis do not have symptoms, there is another problem, as it hinders accurate diagnosis and makes toxoplasmosis a neglected disease (Montoya *et al*., 2004; Storchilo, 2020). The identification of specific antibodies is also an alternative for the diagnosis of toxoplasmosis, combined with serological and parasitological tests (Robert-Gangneux; Dardé, 2012; Storchilo, 2020). Parasitological diagnosis is carried out in reference laboratories, has low sensitivity and is only performed in case of suspected reactivation of the disease (Duarte & Andrade Júnior, 1994; Murat *et al*., 2013; Storchilo, 2020). In this case, the parasite is identified and isolated by inoculation of the suspicious material in animals or in cell culture (Duarte & Andrade Júnior, 1994; Montoya, 2002; Baquero-Artigao *et al*., 2013; Montoya *et al*., 2013; Moral, 2020). In serological tests, toxoplasmosis is confirmed by the identification of IgG and IgM antibodies, as well as IgA to determine the phase of infection (Robert-Gangneux; Dardé, 2012; Storchilo, 2020; Torquato *et al*., 2022). Some surface antigens are also used to make the diagnosis, such as SAG1, SAG2 and SAG3, ROP5 and ROP18 (Pietkiewicz *et al*, 2004; Khanahila *et al.*, 2014; Grzybowski *et al.*, 2015; Storchilo, 2020).

Among the main techniques used for the laboratory diagnosis of toxoplasmosis are those involving molecular biology, especially the numerous variations of PCR (polymerase chain reaction), in the direct method, which consists of amplifying some specific gene of the genetic material of the study material from a *primer*, whose sequence is complementary to a DNA sequence of the same, which is known as the target sequence. The amplification of the sequence occurs through cycles that can vary in duration and temperature, for example, depending on the thermocycler, but consists of standard steps: dissociation of the strands from the target molecule, girdling of the primers, and synthesis of new strands by polymerase action (Weaver, 2001; Colombo *et al*., 2005; Lima, 2008; Baquero-Artigao *et al*., 2013; Souza *et al.*, 2014; Moral, 2020). In the case of *T. gondii*, there are dozens of target sequences described, and among the most widely used are the B1 and AF146527 genes, which are repeated about 35 and 250 to 300 times in the genome, respectively (Burg *et al*., 1989; Homan *et al.*, 2000; Sensini, 2006; Wahab *et al*., 2010; Souza *et al.*, 2014). In the indirect method, most diagnoses are made by identifying anti-T. *gondii antibodies* (Souza *et al.*, 2014; Moral, 2020). For this, the development of other techniques with the use of antibodies was necessary, such as solid phase techniques (e.g. indirect ELISA), where there is a surface coated with antigens and, when added to the sample, in the presence of anti-T. *gondii antibodies*, there will be the formation of an antigen-antibody complex to be accused by a signal emission. which can be a color, which will be detected by a sensor, allowing the evaluation of the reaction (Voller *et al*., 1976; Balsari *et al*., 1980; Souza *et al.*, 2014; Liu Q *et al.*, 2015; Silva, 2022). Table 1 shows the main diagnostic methods.

Table 1: Types of diagnosis for toxoplasmosis and their methodologies.

Diagnosis	**Methodology**
Parasitological	Identification and isolation of the parasite in cell culture
Serological	Identification of antibodies (IgG, IgM, IgA) to determine phase of infection and detection of parasite surface antigens (AG1, SAG2 and SAG3, ROP5 and ROP18)
Laboratory	PCR, which consists of the amplification of a specific gene, such as B1 and AF146527; Indirect ELISA, where there is the formation of an antigen-antibody complex accused by the emission of some signal to be detected by a sensor

3.3) TREATMENT

The treatment against toxoplasmosis, in general, consists of associating antimicrobials capable of inhibiting dihydrofolate reductase and dihydrophate synthetase, thus blocking the synthesis of folic acid. Studies related to the search for new treatments for this disease aim, in general, to produce substances capable of inhibiting important pathways for the metabolism of *Toxoplasma gondii*. Thus, these drugs are able to inhibit the production of enzymes that act in the development of the parasite, such as dihydrofolate reductase, cysteine proteases, and NADH dehydrogenases (Kortagere, 2012; Dunay *et al*., 2018).

Ocular toxoplasmosis affects about 10% of patients who are in the acute phase of the disease and the lesions can vary from milder to more severe, and can even cause blindness (Commodaro *et al*., 2009; Barb *et al.*, 2015; Queiroz *et al.*, 2018; Silva *et al*., 2023). For these aggravating factors of toxoplasmosis, there is still no specific treatment and, therefore, the standard treatment refers to the use of sulfamethoxazole and trimethoprim, drugs that can be associated with anti-inflammatory corticosteroids and eye drops (Holland & Lewis, 2001; Felix, 2015; Silva *et al*., 2023); In addition, in some cases, it is perceived that the association of sulfadiazine and pyrimethamine is also efficient in combating ocular toxoplasmosis, however, the severity of the lesion in these cases is not yet well described, so there is no way to actually confirm the efficacy of this association in the treatment of congenital toxoplasmosis (O'Connor *et al*., 1964; Dunay *et al.*, 2018).

Suppressive therapy aims to reduce the recurrence of the disease, as well as reduce the severity of the lesions; this type of therapy has been shown to be effective in ocular toxoplasmosis in cases of chorioretinitis through the use of the following drugs: pyrimethamine, sulfadoxine, and TMP-SMX (Dunay *et al*., 2018). In immunocompromised patients with toxoplasmic encephalitis, the use of sulfadiazine and pyrimethamine has been shown to be effective, although the treatment may have reduced efficacy due to adverse reactions, such as leukopenia (low white blood cell rate) and rash, to reduce this hematological toxicity, the use of folinic acid in line with the drug is recommended (Haverkos, 1987; Dunay *et al.*, 2018;).

During pregnancy, pregnant women with toxoplasmosis should associate the drugs with folinic acid so that there is no exacerbated toxicity (Neto, 1982; Andrade & Aguiar, 2012; Santa Catarina, 2022). In congenital toxoplasmosis, to avoid the adverse effect of pyrimethamine, the use of spiramycin (during the first trimester of the gestational phase) is indicated, since pyrimethamine is potentially teratogenic for humans, that is, it is possibly a substance that impairs the development of embryonic or fetal life. Spiramycin has no toxic effect and does not cross the transplacental pathway, and is used prophylactically to prevent the transmission of the parasite during pregnancy (Garin & Eyles, 1958; Montoya & Remington, 2008; Andrade & Aguiar, 2012; Dunay *et al.*, 2018). Newborns with congenital toxoplasmosis should receive postnatal treatment, which is capable of preventing the worsening of clinical manifestations, in

addition to preventing the appearance of new symptoms. Treatment can be performed by combining pyrimethamine and sulfadoxine together with folinic acid (Neto, 1982; Teil, 2016; Dunay *et al.*, 2018). It is noteworthy that folinic acid is different from folic acid, since the chemical composition, metabolism pathways, and even the mechanism of action of these two compounds are distinct. Folinic acid can be used to reduce the toxicity of chemotherapy drugs, so its use is recommended. The main drugs used for the treatment of toxoplasmosis are described in Table 2.

Table 2: Types of toxoplasmosis and their respective therapies.

Toxoplasmosis	**Drugs**
Active	Sulfadiazine combined with pyrimethamine, antimicrobials capable of inhibiting dihydrofolate reductase and dihydrophate synthetase
Eyepiece	Sulfamethoxazole and trimethopim plus anti-inflammatory corticosteroids and eye drops, suppressive therapy (pyrimethamine, sulfadoxine, and TMP-SMX)
Gestational	Spiramycin with folic acid (during the first trimester of the gestational phase)
Congenital	Pyrimethamine and sulfadoxine together with folinic acid

3.4) RISK FACTORS

The risk factors associated with toxoplasmosis are related to eating habits, as in the case of the consumption of raw or undercooked meats, lack of basic sanitation, garbage collection and treated water, contact with cats and cleaning of their feces, as well as infection during pregnancy. Immunosuppressed patients who have undergone immunosuppressive treatment, transplanted or infected with HIV are also part of the risk factors (Paraná, 2021; Oliveira *et al.*, 2023). A study conducted in Maranhão, by Moura *et al.* (2020), showed that a low number of pregnant women obtained knowledge about toxoplasmosis, although they had preventive habits. In this study, sociodemographic conditions did not interfere with the risk of infection, but this does not exclude the possibility of an association between the two factors. With this, the importance of more efficient public measures, as well as policies that integrate economic, health, and education issues, becomes evident. In addition, the prevalence of toxoplasmosis is higher in veterinarians and butchers, who work with raw meat on a daily basis, which makes preventive and hygiene measures important in the handling and raising of animals for human consumption (Marinho *et al.*, 2020).

3.5) ASSOCIATION WITH OTHER PATHOLOGIES

Toxoplasmosis can be associated with several neuropsychiatric disorders, as *Toxoplasma gondii* can lodge in different neuronal cells, such as astrocytes, glial cells and neurons, generating lesions that can promote neuroinflammation present in different neurological diseases (Halonen *et al*., 1996; Ortiz-Guerrero *et al*., 2020). Parkinson's, schizophrenia, depression, and Alzheimer's are examples of disorders that may be related to *T. gondii infection*.

Regarding the association between toxoplasmosis and Parkinson's disease, it is clear that the parasite has two genes capable of encoding the enzyme tyrosine hydroxylase (Santos *et al*., 2017). This enzyme is responsible for initiating the synthesis of dopamine, which transforms tyrosine into L-dopa and which, through the action of a decarboxylase, is converted into dopamine (Nicolau & Assis, 1969; Estevinho & Fortunato, 2003). Through the encoding of tyrosine hydroxylase, there is an increase in the production of dopamine and its exacerbated production can lead to a degeneration of dopaminergic neurons, this type of aggravating factor is seen in Parkinson's disease and schizophrenia, although Parkinson's disease is commonly characterized by reduced dopamine levels (Sttibs, 1983; Miman *et al*., 2010; Santos *et al*., 2017).

In addition, it is noticed that patients with schizophrenia are more likely to have antibodies against *Toxoplasma gondii* and that congenital toxoplasmosis increases the chances of having schizophrenia (Fuglewicz *et al*., 2016). Furthermore, parasitic infection can lead to an interruption in the production of tryptophan, which is important in the development of the parasite, but this interruption can generate an accumulation of substances with toxic effects for the body, such as cyanuric acid. This acid is found in the cerebrospinal fluid of some schizophrenic patients and may be associated with the symptoms found in these patients. Other factors prove this relationship between neuropsychiatric diseases and toxoplasmosis, such as the use of psychotropic drugs can contribute to combating the proliferation of *T. gondii* (Pezzella *et al*., 1997; Jones-Brando *et al*., 2003; Fuglewicz *et al*., 2016). Regarding toxoplasmosis and depression, Groër *et al.* (2011) demonstrated that pregnant women who have toxoplasmosis tend to have greater chances of presenting anxiety and depression. The reason for this relationship is not yet consensual, but this association may be related to specific endocrine mechanisms, since in patients with toxoplasmosis, there is an increase in testosterone levels. This increase may be related to a suppression of immune system responses, in addition to contributing to depression in women (Flegr, 2007; Groër *et al.*, 2011). It should be noted that the mechanisms involved in this correlation are not yet fully elucidated (Shiadeh *et al*., 2016; Santos *et al*., 2017).

The inflammatory responses that occur during *Toxoplasma gondii* infection may be related to the association between toxoplasmosis and Alzheimer's disease. To combat this parasite, Th1 cells release different cytokines that have a cytotoxic effect, such as IL-12, IFN-γ, IL-6 and tumor necrosis factor (TNF), these cytokines can cause damage to neurons that have not been infected by *T. gondii*, resulting in damage to neurotransmitters and synaptic transmission

(Tancredi *et al*., 1992; Dunn, 2006; Nayeri *et al*., 2021). IFN-γ can act on the destruction of neurons that synthesize dopamine and it is worth mentioning that in the pathology of Alzheimer's and Parkinson's, there is a decrease in dopamine levels. This decrease in dopamine production can also be achieved by *T. gondii* through its mechanisms capable of affecting the expression of micro-ribonucleic acids-132 (miR-132) and this alteration can also be correlated with the characteristic symptoms of Alzheimer's (Prandovszky *et al*., 2011; Miller *et al*., 2012; Nayeri *et al*., 2021). All neuroinflammatory processes resulting from *T. gondii infection* can generate common damage in the pathogenesis of Alzheimer's and Parkinson's disease (Lee *et al*., 2010; Querfurth & LaFerla, 2010; Jung *et al*., 2012; Santos *et al*., 2017).

Studies related to the association of Toxoplasmosis and other pathologies, especially neuropsychiatric pathologies, are very recent, therefore, it is clear that the results obtained in the main studies are not very conclusive and, in some cases, present controversies. Thus, it is necessary that more research be carried out in this area so that there is a better elucidation of these associations.

The parasite can remain latent in the Central Nervous System in the form of a cyst containing bradyzoites, but these cysts can rupture and the bradyzoites are converted into tachyzoites, resulting in the infection of neuronal cells and inducing neuronal degeneration and pro-inflammatory effects (Minto & Roberts, 1959; Buitrago *et al*., 2024). The possible associations and their mechanisms are described in Table 3.

Table 3: Diseases associated with toxoplasmosis and description of their possible mechanisms.

Diseases	**Possible mechanisms associated with toxoplasmosis**
Parkinson	Encoding the enzyme tyrosine hydroxylase, involved in the process of dopamine synthesis
Schizophrenia	Disruption of tryptophan synthesis, which can lead to accumulation of toxic substances found in patients with schizophrenia
Depression	Increased testosterone levels in pregnant women, which reduces the immune response; mechanism not yet fully elucidated
Alzheimer	Cytokines released by the immune system to fight *T. gondii* can cause damage to dopamine-producing neurons, generating the characteristic signals

3.6) FUTURE PROSPECTS

Recent studies seek to find compounds with anti-toxoplasma activity as an alternative method to conventional treatment. The paper published by Cardoso *et al*. (2022) characterized new compounds for the treatment of toxoplasmosis containing Cu(II), Fe(III) and Zn(II), these compounds demonstrated cytotoxic effects on *T. gondii*, reducing the parasite's ability to proliferate. These results suggest that these compounds are promising, leading to parasite death.

There are still no vaccines for humans that can prevent against toxoplasmosis. However, many studies have shown prospects for advances in vaccine production, especially in cases of congenital toxoplasmosis. Attenuated vaccines, i.e., vaccines that use the parasite with reduced virulence, are not yet licensed for use in humans due to the risks of protozoan reactivation and because they do not have long-lasting efficacy (Zhang *et al*., 2014; Barros *et al*., 2021). Vaccines that use DNA are widely researched in relation to toxoplasmosis, demonstrating positive results, but more studies on their effectiveness should be carried out. Another problem related to the production of vaccines to prevent the transmission of congenital toxoplasmosis refers to the ineffectiveness in total protection of all the vaccines tested (Barros *et al*., 2021).

3.7) GRAPHIC ANALYSIS:

A total of 1,303,886 articles were found related to the terms described in the methodology for the production of the article. The figures below show the total number of articles found for each term and the respective platforms used.

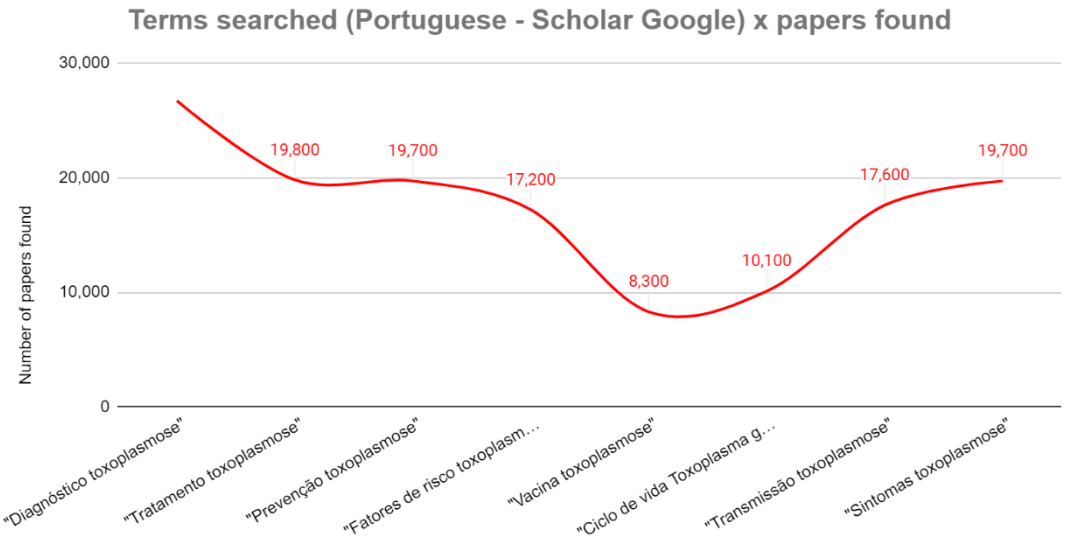

Figure 1: Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis symptoms", "toxoplasmosis diagnosis", "toxoplasmosis treatment", "toxoplasmosis prevention", "toxoplasmosis risk factors", "toxoplasmosis vaccine" in

Portuguese. A quantitative analysis was carried out on the articles found on the "Google Scholar" platform, having been searched on 03/13/2024 at 14:23h. Total: 139,100.

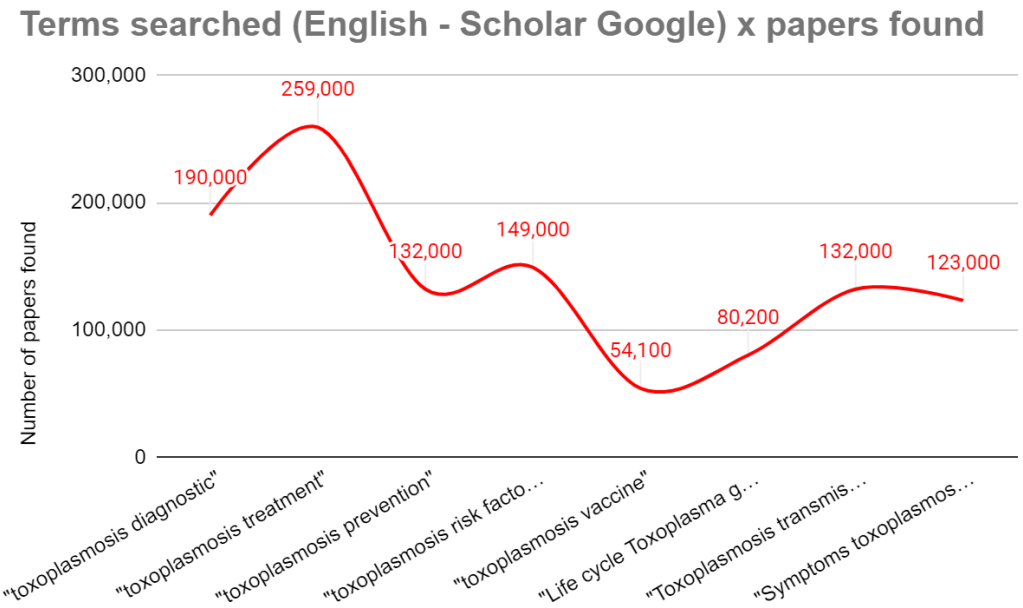

Figure 2: Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis symptoms", "toxoplasmosis diagnosis", "toxoplasmosis treatment", "toxoplasmosis prevention", "toxoplasmosis risk factors", "toxoplasmosis vaccine" in English. A quantitative analysis was carried out on the articles found on the "Google Scholar" platform, having been searched on 03/13/2024 at 14:28h. Total: 1,119,300.

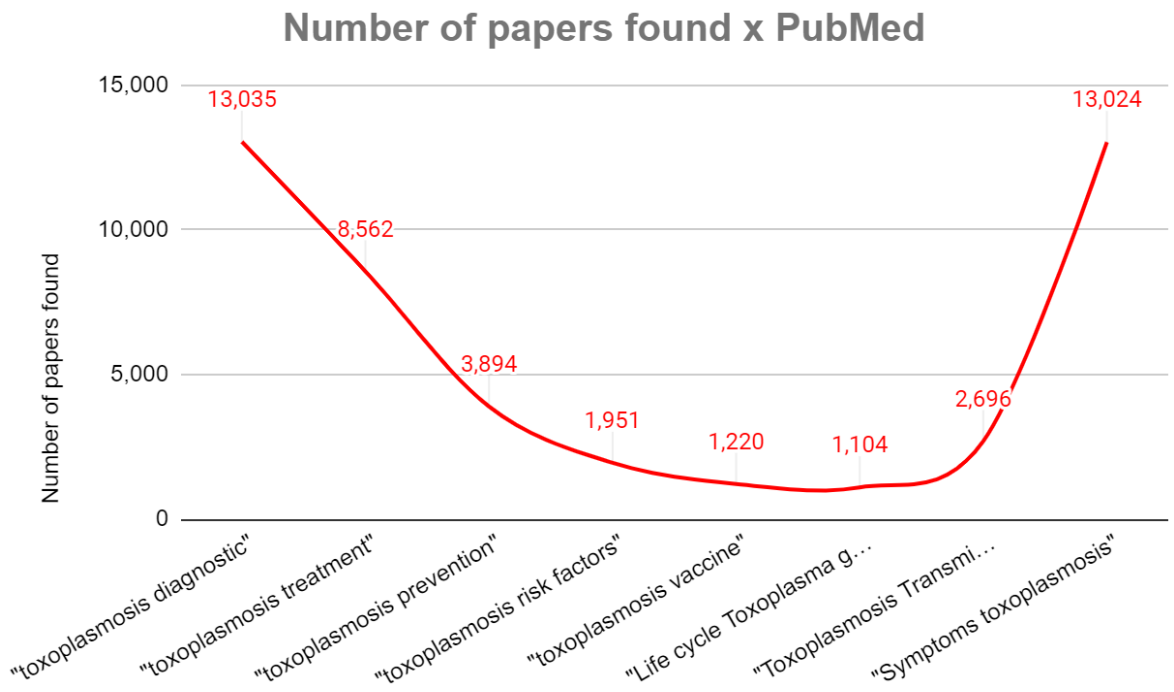

Figure 3: Articles found using the terms "*Toxoplasma gondii* life cycle", "toxoplasmosis transmission", "toxoplasmosis symptoms", "toxoplasmosis diagnosis", "toxoplasmosis treatment", "toxoplasmosis prevention", "toxoplasmosis risk factors", "toxoplasmosis vaccine" in English. A quantitative analysis was carried out on the articles found on the "*PubMed*" platform, and they were searched on 03/13/2024 at 2:32 pm. Total: 45,486.

4) DISCUSSION:

Tables 1, 2, and 3 show, respectively, the diagnosis, treatment, and association of the mechanisms of toxoplasmosis with other diseases. Regarding the diagnosis, it is clear that the methodologies are well established, with direct and indirect methods for the identification of the parasite in the body, with the serological test being the most used, in view of the cost-benefit ratio and also less need for technical preparation. Laboratory diagnosis is essential for the identification of fetal toxoplasmosis, and a sample of amniotic fluid is extracted. Combined with an early diagnosis, the start of toxoplasmosis treatment should be carried out as soon as possible, to prevent the progression of the disease and, consequently, avoid sequelae, especially in immunosuppressed patients or those who have acquired or may acquire toxoplasmosis congenitally. The treatment schedule depends on the type of toxoplasmosis and gestational age, avoiding teratogenic effects. Studies that relate the mechanisms of toxoplasmosis with the emergence of neurological diseases are recent and, therefore, the data may not be conclusive, although they can be associated.

Regarding the graphs, it is observed that, in the Portuguese language, on the Google Scholar platform, there are few publications related to the searched terms, which differs from the terms selected for research in English, on the same platform, with the difference being approximately 980,200 articles. In PubMed, there are also few publications about the searched terms, this number being close to 45,500. On Google Scholar, both in English and Portuguese, the terms that refer to the toxoplasmosis vaccine are the ones with the lowest number of articles, suggesting the difficulty of research on the subject.

5) CONCLUSION:

Based on the above, it is possible to conclude that the best way to prevent toxoplasmosis is through information and awareness of the population about the risks of the disease and management of possible contaminants. Although the disease has a well-defined diagnosis, it still needs more studies directed, mainly, to new treatments, since the usual therapies are still quite limited and cannot eliminate the parasite from the host.

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