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TÍTULO: Una revisión actualizada de Toxoplasma gondii en Ecuador: dónde estamos y a dónde vamos desde aquí.

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RESUMEN: Toxoplasma gondii es un parásito apicomplejo extremadamente exitoso, que es capaz de invadir virtualmente cualquier célula nucleada. T. gondii tiene una seroprevalencia global estimada del 30% en la población humana. Dentro de un huésped inmunocompetente, este parásito no causa ningún daño a los sistemas internos; in embargo, en los casos de transmisión congénita durante el embarazo o de reactivación de la infección en pacientes inmunodeprimidos, la infección por T. gondii representa una amenaza potencialmente grave. Aquí, mostramos una revisión de la literatura dirigida a estudiar el estado de T. gondii y la toxoplasmosis en el Ecuador.

PALABRAS CLAVES: Toxoplasma gondii, toxoplasmosis, Ecuador, toxoplasmosis congénita, toxoplasmosis adquirida.

TITLE: An updated revision of Toxoplasma gondii in Ecuador: where we are and where we go from here.

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ABSTRACT: *Toxoplasma gondii*is an extremely successful apicomplexan parasite, which is able to invade virtually any nucleated cell.*T. gondii*hasan estimated global seroprevalence of 30% inhuman population.Within an immunocompetent host, this parasite causes no harm to the internal systems; however,in cases of congenital transmission during pregnancy or reactivation of infection in immunosuppressed patients, *T. gondii* infection representsa potentially serious threat. Here, we show a literature review aimed at studying the state of *T. gondii* and toxoplasmosis in Ecuador.

KEY WORDS: *Toxoplasma gondii*, toxoplasmosis, Ecuador, congenital toxoplasmosis, acquired toxoplasmosis.

INTRODUCTION.

Toxoplasma gondii, the causative agent of toxoplasmosis,is an apicomplexan protozoan parasite, whoselife cycle requiresa definitive host, felines (including domestic cats), and an intermediate host,which can be any warm-blooded animal such as birds or mammals(Bintsis, 2017).

During its development, *T. gondii*passes through three infective stages: tachyzoites, bradyzoites and sporozoites. In fact, intermediate hosts, including human beings,canbe infected withany of these three stages; for instance, sporozoites are shed to the environment via cat faeces where the parasites can get in contact with water, fruits, and vegetables. From this point, parasites can enter to the intermediate host and become tachyzoites once inside.

The tachyzoite stage is characterised byits ability to glide, infect, and replicate inside host cells in a rapid manner (Hill & Dubey, 2018). When extracellular, tachyzoites can be supressed by the immune system or by using drugs like sulfadiazine and pyrimethamine (McLeod et al., 2014;

Paquet et al., 2013); however, after several rounds of replication, tachyzoites undergo a transition to bradyzoites, a dormant stage which develop into cysts insidecells. Once this stage is reached treatment of the infection is complicated because the parasites areeffectively hidden from the immune system and more resistant to chemotherapy with drugs (Wohlfert, Blader, & Wilson, 2017). Humans are not part of the natural life cycle of the parasite, but canacquire the parasite in different ways: by contact or ingestion of contaminated soil, food and/or water, by transfusion of blood and/or organs containing the parasite, via transplacental infection, or by accidental inoculation (Kijlstra & Petersen, 2014).

T. gondii infections are common across every continent. Aglobal analysis of human toxoplasmosis estimates that *T. gondii* seroprevalence varies between 10%-90% of the population across different regions(Pappas, Roussos, & Falagas, 2009), with the majorityof cases being asymptomatic in acute and chronic stages. Still, a small percentage of acute infections can present flu-like symptoms, hepatosplenomegaly, or lymphadenopathy (WHO, 2001).On the contrary, suppression of the immune system can induce the activation and conversion of the bradyzoites to rapidly moving tachyzoites, which triggers their dissemination to different tissue types. Under this circumstance, the parasites can infect virtually any nucleated cell, such as those in the lungs and brain, causing serious damage to the cellular structures of the host. In addition, infection of women during pregnancy can lead to severe damage to the foetus or miscarriage (Torgerson & Mastroiacovo, 2013).

T. gondii populations are classified in three main lineages called type I, II, and III (Dard, xe, L., Bouteille, & Pestre-Alexandre, 1992; Howe & Sibley, 1995). Experiments carried out in laboratory mice showed that type I strains are more infectious and cause severe acute toxoplasmosis compared to type II and type III strains (Dubey, Ferreira, Martins, & McLEOD, 2012). Type I strains are mostly found in South America, where toxoplasmosis is highly prevalent, more aggressive, and is

the causative agent of severedamage in both congenital and acquired infections. Likewise, a recent study suggests that *T. gondii*diverged in South America due to the presence of a great variety of wild felines and murids via carnivorism, which contributed to the transmission adaptation in this area(Bertranpetit et al., 2017). Altogether, this data suggests an existing association between the virulence, geographic area, and *T. gondii* lineage.

A plethora of studies have shown the impact of toxoplasmosis in South America. For instance,a review of toxoplasmosis cases in the last 70 years in Colombia concluded that this infection remainsan important health problem (Cañón-Franco, López-Orozco, Gómez-Marín, & Dubey, 2014). Similarly, the presence of *T. gondii* in different Brazilian provinces showsthat the population is at high risk to acquire the infection and develop serious health problems (Grigg, Dubey, & Nussenblatt, 2015). Considering the available information of neighbouring countries, it is highly possible *T. gondii* and toxoplasmosis status in Ecuadoris related to these areas.

The aim of the present paper is to analyse the current situation of *T. gondii* in Ecuador by analysing published data of seroprevalence in the population. Also, this publication revisits the mainfactors that could influence toxoplasmosis prevalence. Finally, based on the scientific response of different countries to *T. gondii* presence, here we present recommendations to develop future studies focused on this pathogen.

DEVELOPMENT.

Methods.

Published studies were identified by searching different literature databases including Medline via PubMed, Google Scholar, and SciELO. “Toxoplasma [or] Toxoplasmosis” and “Ecuador” were used as key words to select papers without time limitation. Published peer-reviewed papers and postgraduate theses written in Spanish and English were considered in the pool of data. All papers

matching the search criteria were analysed in an individual manner. The search was executed on 27/04/2020 and last updated on 27/05/2020.

Results.

Main information about Ecuador.

Ecuador is a country located in the western side of South America, bordering with Colombia in the north/east, Peru in the south/east, and the Pacific Ocean in the west. This country possesses four main regions: the coastal region, andean region, tropical rain forest, and the Galapagos Islands. These four regions occupy a total area of 276,841 km^2, and present differentgeographic, ecological, and environmental characteristics; for instance, the Galapagos islands, coastal region, and the rain forest possess a tropical climate while the inland Andes highlands are temperate due to the increased altitude. The territory is divided into 24 provinces withEsmeraldas, Manabí, Los Ríos, Guayas, and El Oro in the coastal region; Carchi, Imbabura, Pichincha, Cotopaxi, Tungurahua, Chimborazo, Bolívar, Cañar, Azuay, and Loja in the Andean region; Sucumbíos, Napo, Pastaza, Orellana, Morona Santiago and Zamora Chinchipe in the rain forest; and finally, the Galapagos islands (Figure 1).

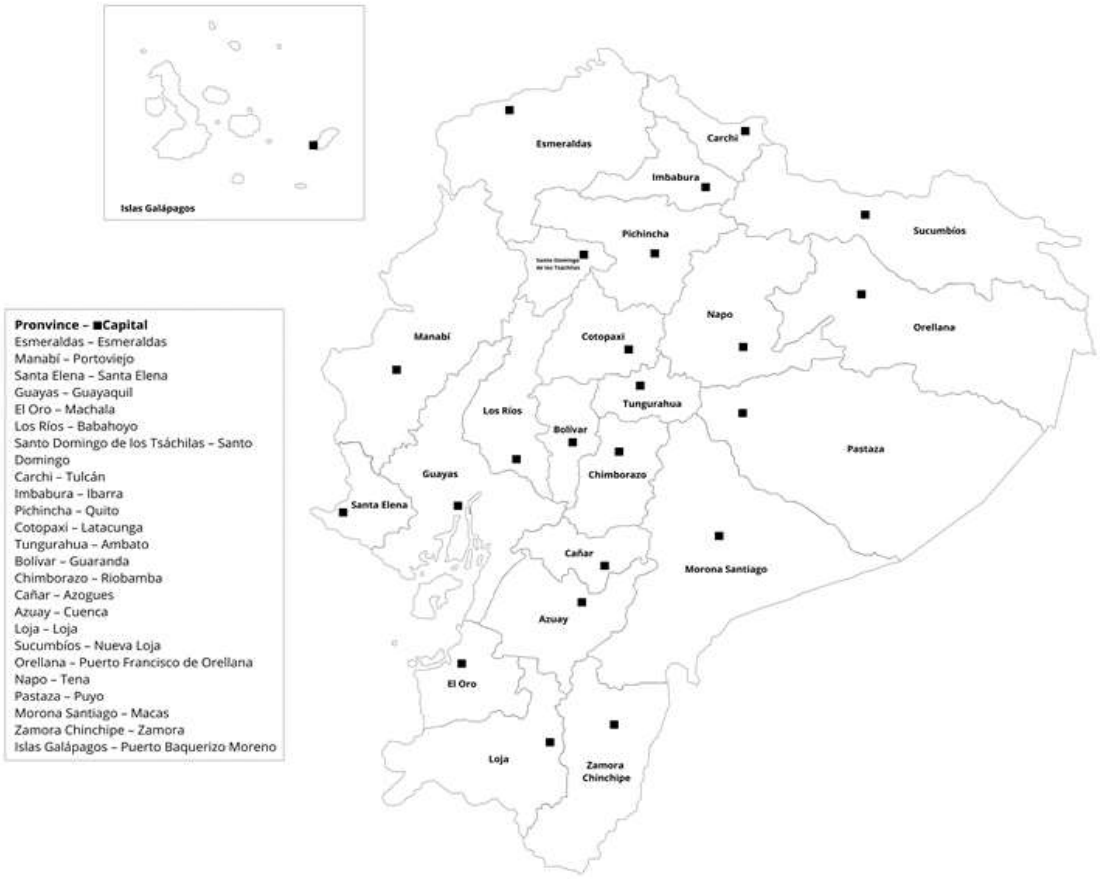

Figure 1. Political Map of Ecuador.

Ecuador is a country located in the north of South America surrounded by Colombia in north-east, Perú in south-east and the Pacific Oceanin west. This country is divided in 24 provinces shown in the graphic. The provinces capitals are marked with a square in the map.

The Ministry of health in Ecuador (MSP) guarantees free access to the public health system to all Ecuadorian citizensregardless of which province they reside in. In order to organizethis service, MSP divided the Ecuadorian territory intonine zones.

Toxoplasmosis in humans.

Human toxoplasmosis was first described in new-born infants who presented neurological impairment (Janku, 1923; Wolf, Cowen, & Paige, 1939). Since then, clinical manifestations of *T. gondii* infection have been described in different tissues and organs. The most commonly

documented are the ophthalmologic and neurological affections in congenitally infected infants and immunosuppressed patients (McLeod, Cohen, Dovgin, Finkelstein, & Boyer, 2020).

Ocular toxoplasmosis.

T. gondii infections can cause ocular impairment through scarring and inflammation of the uvea and the retina (Pfaff et al., 2014). These inflammations are more frequently reported in postnatally infected patients than congenitally infected ones (Garweg, 2016). Ocular toxoplasmosis is observed globally, with a higher incidence in tropical areas (Huang et al., 2018). Furthermore, reports of this infection in Central and South America describe more severe manifestation in the ocular tissue (Diaz, Bustillo, Pacheco, & Gritz, 2016; McLeod et al., 2020). In fact, a study published in 2008 found that Brazilian children suffering with ocular toxoplasmosis possess five times higher risk to develop larger and more severe lesions in the eyes when compared to European children (Gilbert et al., 2008).

Applying the stated search parameters only one published paper describing two cases of ocular toxoplasmosis in Ecuador was found. In this report, the authors detected the presence of parasites in the ocular tissue of the patients usinganti *T. gondii* IgG and IgM antibodies. The results suggest that both patients were suffering from active ocular toxoplasmosis which resulted insevere chorioretinitis and loss of unilateral visual acuity.Furthermore, the analysed patients presented no apparent immunodeficiency. However, no further details of treatment or case tracking were reported (González Delgado, 2010).

Toxoplasmosis in immunodeficient patients.

The reduction or impairment of the immune responsein patients is a contributing factor for latent*T. Gondii* reactivation. In fact, a deficient immune system triggers rapid dissemination and reproduction of the parasites inside the patients, generating severe multi-organ infections with

potentially fatal consequences. Considering these factors, the most vulnerable groups of people are those suffering from human immunodeficiency virus(HIV)/acquired immunodeficiency syndrome (AIDS), cancer patients, and transplant recipients (Abdoli, Barati, Dalimi, Pirestani, & Hoseini Shokouh, 2016).

The MSP estimates that the number of people infected with HIV was 0.22per 1000 inhabitants in 2017 (MSP, 2020b). In the same year, the MSP reports that the number of patients with AIDS in the country was 36.544, with higher prevalence in men between 15 and 49 years of age (MSP, 2020b).

A report published in 2019 presented the socioeconomic factors of 100 adult patients infected with HIV and who were diagnosed with encephalic toxoplasmosis (Carrillo Pincay, Chiu Yen, Robles, & Moreira-Holguín, 2019). This research was conducted in two major regional hospitals that receive patients from different provinces of the country. Data analysed in this study was retrieved from medical records; thus, only fully filled records were considered. The authors reported that the main manifestations of the infection at the neurological level among the patients were frontal and parietal lobe signs, convulsive syndrome, and cranial nerve paralysis.Additionally, using statistical analysis, this study showed that HIV/toxoplasmosis comorbidity is strongly associated with a rural population with scarce access to education or public health (Carrillo Pincay et al., 2019).

A recent study carried out in 816 HIV/AIDS patients reported that 72 of them suffered from toxoplasmic encephalitis, representing 8.8% of this set(Vasquez, Monserrate, Lalangui, & Chacán, 2020). Clinical manifestations presented by these patients were headache, fever, convulsions, and loss of consciousness. Further, the study reported that 5 of the 72 patients died as a result of complications due to rapid disease progression (Vasquez et al., 2020). The authors noted that a limitation of the study was the occurrence of incomplete or missing medical records and serology results (Vasquez et al., 2020).

Based on the current literature review, only one study detected *T. gondii* in cerebrospinal fluid using molecular markers (Acevedo et al., 2017). This experiment was carried out by a group of scientists researching the incidence of Zikaand Dengue virus in 16 patients admitted to a major hospital in Guayaquil city. The results described one case of an HIV/AIDS patient coinfected with *Toxoplasma* (Acevedo et al., 2017). This patient was diagnosed with encephalitis and showed symptoms including fever, headache, weakness, anorexia, and neck stiffness. No more data about this finding was reported (Acevedo et al., 2017).

A clinical case of a patient native to the coastal region of Ecuador shows development of ocular toxoplasmosis in an HIV/AIDS patient with leishmaniasis. The patient presented unilateral retinochoroiditis and uveitis, typical signs of *T. gondii* infection reactivation. The presence of this pathogen was confirmed using serological tests (Calvopina et al., 2017).

The prevalence of *T. gondii* infections associated with other pathologies are reported in Ecuador. For instance, toxoplasmosis wasdetected via serological tests in a patient diagnosed with sinus histiocytosis, also called Rosai-Dorfman disease (Zambrano, Mosquera, Vivar, & Diaz, 2019). This is a rare and benign condition characterised by a rapid production and accumulation of histiocytes in the lymphatic nodes, causing lymphadenopathy (Dalia, Sagatys, Sokol, & Kubal, 2014).

The cause of sinus histiocytosis is not well understood, but many cases are associated with immunodeficiencies, chronic infections, and autoimmune diseases (Dalia et al., 2014). In the aforementioned case, the patient was a young adult suffering from recurrent adenomegaly and skin rash. Even though *T. gondii* presence was confirmed, no further details about the infection were explored (Zambrano et al., 2019).

Congenital toxoplasmosis.

Vertical transmission of *T. gondii*is reported around the globe. This can be acquired by primary infection of pregnant women, by the reactivation of a latent infection in immunocompromised pregnant women, and by infection of women shortly before pregnancy (Lindsay & Dubey, 2011). According to the literature, *T. gondii* tachyzoites invade uterus cells and subsequently pass, first to neighbouring cells, and eventually, to the foetus or embryo (Robbins, Zeldovich, Poukchanski, Boothroyd, & Bakardjiev, 2012).

The signs and symptoms of congenital toxoplasmosis are highly variable (McAuley, 2014). Some of the clinical manifestations reported are spontaneous abortion, prematurity, chorioretinitis, hydrocephaly, or microcephaly, cranial calcification, convulsions, abnormal cerebro-spinal fluid, hepatosplenomegaly, myocarditis, pneumonitis, respiratory problems, lymphocytosis, monocytosis, nephrotic distress, and malformations (McAuley, 2014).

The prevalence of congenital toxoplasmosis in the USA is around 1 in every 3000-10.000births (Jones et al., 2001; McAuley, 2014). In Colombia, this prevalence is estimated torangearound 1in every 900-1800 births (Cañón-Franco et al., 2014). Moreover, the prevalence of *T. gondii* infections in pregnant women varies among countries in Latin America. For instance, Colombiareports an incidence of47-54.6%, Perú shows an incidence of 15-30%, and Venezuela ranges between 20-40% (Cañón-Franco et al., 2014; Fernandez, Acosta, & Montano, 2011).

In Ecuador, some studies report cases of congenital *T. gondii* transmission. According to a study published in 2002 by the Instituto Nacional del Niño y la Familia (INNFA) in Portoviejo city, one of the causes of paralysis due brain damage in children attending this institute is vertical transmission of*T. gondii*. This project examined 127 children, of whom 2 presented with congenital toxoplasmosis (1.57%) (Barreiro, Mendoza, Medina, & Pinargote, 2002).

Two reports published in 2007 and 2011 describe five clinical cases of children with congenital toxoplasmosis in Guayaquil and Portoviejo, respectively (Correa, Suárez, & Orozco, 2008; Fernandez et al., 2011). In these studies, acute infected patients presented with hydrocephaly, strabismus, visual and motor disabilities, bone calcification, neuro-ophthalmic infections, and blindness due to bilateral chorioretinal scars (Correa et al., 2008; Fernandez et al., 2011).One patient diedat age 3 shortly after being diagnosed due to the continued progress of the infection(Fernandez et al., 2011).

MSP publishes a weekly epidemiological gazette that reported that the cases of toxoplasmosis in pregnant women tripled in a period of twelve weeks in 2013 in Ecuador (MSP, 2013). In addition, this information suggests that the incidence of this infection is higher in women between 20 and 35 years old. However, reports of risk factors among women or incidence of vertical transmission are not included. Regardless, toxoplasmosis cases in the country have not been reported since (MSP, 2013, 2018).

There were 51 cases reported among women aged 20 to 35 years by the Weekly Epidemiological Gazette Number 16 in 2013 (Velásquez Serra, et al., 2019). In 2008, the Gyneco-Obstetric Hospital Isidro Ayora found a 71.4% infection rate in adolescent mothers aged 34 years or younger in Quito. In 2014, El Oro reported an incidence of 18,8% from 250 pregnant women between 14 and 50 years. Among these, 50% of cases with antibodies were in women between 26 and 30 years of age, and 28% in women between 21 and 26 years (Velásquez Serra, et al., 2019).

A recent review aimed at recording the incidence of vertical transmission of *T. gondii*in Ecuador. The analysed studies suggest a high percentage of toxoplasmosis in pregnant women in different cities around the country (Serra et al., 2020). For instance, one study found 74% of women living in different cities in the coastal region, including Guayas, El Oro, and Manabí are seropositive (Fernandez et al., 2011; Serra et al., 2020). Similarly, in the Andean region of Ecuador the

percentage of pregnant women infected with *T. gondii*varies from 30 to 75% in cities like Quito, Cuenca, and Riobamba (Serra et al., 2020).

Discussion.

Toxoplasmosis represents a realhealth threat to immunocompromised individuals, pregnant women, and new-born children worldwide. A plethora of studies have suggested that *T. gondii* virulence is strongly associated with geographical area, with SouthAmerica representing a hot spot with some of the most virulent strains (Bertranpetit et al., 2017; Hosseini et al., 2019; Khan et al., 2011; Sibley & Boothroyd, 1992; Su et al., 2012; Xiao & Yolken, 2015).

Reports in patients and samples from Brazil, Colombia and Argentina have contributed to understand the strain variability and toxoplasmosis severity among different regions all over the world (Grigg, Dubey, & Nussenblatt, 2015; Hosseini et al., 2019; Shwab et al., 2018). Nevertheless, samples and strain of Ecuador are still unknown, confirming that the state of toxoplasmosis in Ecuador is still understudied.

Through our extensive literature review, we highlight the lack of continuous studies to report and trace toxoplasmosis cases in the country. Although surveillance of the disease is reported in some studies, there is no available information of the infection rate within the country as a whole; for instance, most of the information retrieved in this literature revision was in regard to the coastal region of Ecuador, with a bias towards major cities. Conversely, the incidence of toxoplasmosis in the Andean region is only sporadically reported and is only available for large cities such as Quito and Cuenca. In addition, the presence of the parasite is primarily being elucidated using serology (IgG/IgM), with only a few exceptions involving molecular detection. The use of different technologies for detection must be considered in order to obtain robust and accurate results.

Another issue described in the retrieved papers is the reduced or incomplete information present in the clinical records of the patients. As mentioned in the studies, this factor limited the capacity of the researchers to fully infer the real state of each patient. In addition, this lack of information may result in poor control and tracking of possible complications in patients affected by toxoplasmosis. Consequently, the diagnosis, development, and treatment of these patients may be precarious, insufficient, orotherwise inadequate.

It is important to highlight that this study included only peer-reviewed literature. Thus, academic works that did not pass through a peer-review process were not considered in this analysis.

Where to go from here?

Given this paucity of data, it is still possible to infer that, in terms of toxoplasmosis, Ecuador likely presents the same factors as those affecting neighbouring countries such as Colombia, Perú, and Brazil. Considering this, we propose below how to develop studies within the country on *T. gondii*. as an important pathogen and as the causative agent of toxoplasmosis.

Knowing the pathogen.

Given that a large number of a typical *T. gondii* strains are known to be present throughout South America, we strongly suggest developing studies to detect and characterise circulating strains using molecular methods. This is especially important in light of the known correlation between genotype and disease severity within *T. gondii* strains. A full characterization of the native strains necessitates collecting and sequencing their DNA. Coincident with these sequencing efforts, it is also necessary to characterize the pathogenicity of all identified strains used both *in vivo* and *in vitro* assays. Notably, the collected data of these studies must be compared among different regions of the country due to the great variety of environmental, geographical, ecological, and social factors among the regions.

Another underdeveloped area of research regards the sources of *T. gondii* infection. As mentioned in the introduction, *T. gondii* goes through three infective stages throughout its life cycle, which increases the number of potential infection routes. For example, the water reservoirs supplying cities and towns should be tested for *T. gondii* cysts. Similarly, water used to irrigate fruit and vegetable crops is a potential source of contamination, and hence should be evaluated in a similar manner. Furthermore, assessment of *T. gondii* prevalence in meat products can provide important information for use by government entities, municipal administrations, industry associations, and the general population. The development of reliable detection methods in meat products will allow for the production of protocols throughout the production chain to increase the safety and quality of the resulting products.

Understanding the disease.

The mechanisms underlying the increased pathogenicity of atypical strains in South America remains poorly understood. Here, as the disease severity associated with infection by atypical strains is known to be more severe, it is crucial that patients infected with such strains are given adequate medical attention. In order to improve diagnosis and treatment, it is recommended to study the immune system with special emphasis on the development of protective responses. Additionally, the modulation of the host immune response should be comparedbetween patients affected by congenital and acquired toxoplasmosis.

1. We consider the development of research projects aimed to study and track inflammation progression during either congenital or acquired toxoplasmosis to be of great importance. Of note, the severity and distribution of lesions in the organs of patients may yield further insights into the biology and expected disease course of *T. gondii* strains circulating in Ecuador.

2. Medical treatments to supress *T. gondii* infection is another interesting area of research. Patients infected with *T. gondii*develop different responses to medical treatments. For this reason, we propose the development of projects to study, track and compare the progress of treatments in different groups of patients. This data could significantlyimprove treatment efficacy.
3. Given that many studies reported limitations due tothe lack of information present in clinical records, here we recommend the development of a standard mechanism to report *T. gondii* infectionsin public and private health services. In addition, in order to advance toxoplasmosis studies and statistical analysis of factors associated to the infection, it is appropriate to publish annual information about toxoplasmosis cases for a sufficient period of time.
4. Health system data collected annually by MSP can be used together with epidemiology data to assess the main risk factors associated with toxoplasmosis in the Ecuadorian population. Thishorizontal study requires the participation of health system workers, physicians, and researchers. For this reason, we suggest developing collaborative efforts in order to achieve progress in the study of this disease.

CONCLUSIONS.

Infection caused by *T. gondii* is present in Ecuador, reinforcing the factthat there are circulating strains in the country. However, studies focused on describingtoxoplasmosis in patients are limitedand no information regarding the strains causing infectionsare registered.

Ocular toxoplasmosis, the major infection caused by *T. gondii*in neighbouring countries, is poorly studied and understood in Ecuador. Two reports present cases of this pathology, but further studies consideringlarger sets of data over a longer period of time are required in order to make informed inferences.

Toxoplasmosis in immunosuppressed patients is another area of research that requires attention. A major limitation recorded in all studies is the lack of complete information in patients' clinical histories,which complicates understanding of the disease. Many patients are diagnosed when the infection has already caused severe damage, affecting the patient'squality of life and overall health. A better understanding of the progress of infection is essential.

This paper presents a set of suggestions to reinforce and increase the understanding of *T. gondii* and toxoplasmosis.However, insights from other professionals and research groups interested in this subject are expected.

Finally, we encourage the establishment of multidisciplinary teams in medical, research, and social disciplines to pursue the revision and impact of this disease in the country.

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