

# Toxoplasmosis in South Africa- Old Disease in A New Context

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## Abstract

Toxoplasmosis is one of the most widespread parasitic infections known. Clinical manifestation of toxoplasmosis because of immunosuppression is typically due to a reactivation of a chronic infection. According to the UNAIDS 2008 report on the global AIDS epidemic, about 5.7 million South Africans were infected and living with HIV in 2007, with obvious risk and health resource implications for toxoplasmosis. *T. gondii* has been largely neglected as a health risk to the general population in the HIV era. Currently South Africa is burdened with ongoing HIV and TB pandemics. South Africa accounts for 17% of the global HIV burden and has a TB incidence of 950 per 100,000 as at 2012. Such high incidence of immunosuppressive infections puts the population at a high risk of opportunistic infections such as toxoplasmosis. Seroprevalence rates in Africa are high in both human and animal populations, but there are no reports on the significance of the pathogen within the food or water chain of African cultures. Future work should focus on a more systematic approach towards *Toxoplasma gondii* seroprevalence data gathering and analysis in order to inform on effective approaches to its prevention and disease reduction, and on the molecular epidemiology of the pathogen within the South African context.

**Keywords:** *Toxoplasma gondii*, behavior, toxoplasmosis, mental health, sero-prevalence, South Africa, disease burden, HEU, HUU.

## 1. Introduction

Toxoplasmosis, a disease caused by *Toxoplasma gondii*, is one of the most widespread parasitic infections known. It has a global distribution, is able to infect nearly all mammalian and avian species and approximately 25% of the global human population is thought to be infected (Fuks et al., 2012).

*T. gondii* has both medical and veterinary significance owing to manifestations such as congenital infections as well as abortions in its human and animal hosts (Kim and Weiss, 2004). Interest in toxoplasmosis and its pathogenesis has resurfaced since it was discovered that with the onset of the acquired immunodeficiency syndrome (AIDS) epidemic, opportunistic infections such as acute toxoplasmosis induced cranial calcification and the ensuing encephalitis could be fatal if not treated (Bhopale, 2003) (Kistiah et al., 2011). The predominant thinking is that parasite transmission in humans and animals is via active or passive ingestion of the persisting stages of the organism (namely the oocysts from feline feces) in contaminated food or water and tissue cysts in infected (contaminated) meat or offal (Frenkel, 1970) (Jacobs and Mason, 1978) (Smith, 1993) (Tenter et al., 2000). Infected felids are known to shed millions of oocysts into the environment through their feces, which then develop into sporulated cysts, which become sources of infection. Not unexpectedly, toxoplasmosis is virtually absent in islands which are uninhabited by felids (Munday, 1972) (Wallace, 1969).

## 2. Pathogenesis

The majority of exposed human adults do not develop apparent clinical symptoms, however, a minority of apparently healthy persons who acquire primary *T. gondii* infection after birth may exhibit mild symptoms such as fever and lymphadenopathy. Recent research suggest that this variability in human infection may in part be ascribed to the causative *T. gondii* strain type (Kim and Weiss, 2004). The infection progresses from an acute stage to a chronic or supposedly latent (cyst) stage in the host (Bhopale, 2003). Infected individuals remain asymptomatic unless they become immunosuppressed. However in certain unusual cases, previously healthy individuals have been known to acquire and develop severe and fatal toxoplasmosis, with pulmonary and multivisceral clinical presentations which are possibly related to virulence of the parasite (Demar et al., 2007). Healthy subjects may also develop ocular complications with severe visual impairment (Glasner et al., 1992) (Dubey and Jones, 2008).

Congenital toxoplasmosis, as the second most common intrauterine infection, remains a public health problem throughout the world. It can result in some of the most serious consequences with a wide range of clinical manifestations, including, but not limited to, spontaneous abortions and stillbirths or in live infants hydrocephalus, microcephaly, and retinochoroiditis and cerebral calcifications. 70-90% of congenitally infected infants are asymptomatic at birth but affected neonates may already demonstrate central nervous system involvement and related complications or an apparently healthy child may present with retinochoroiditis,

chorioretinitis and central nervous system complications later in life (Dubey and Jones, 2008).

The risk of transplacental transmission of *T. gondii* to the developing fetus is low when maternal primary infection occurs during the first three months of the pregnancy (10-15%) and is highest when the primary infection occurs during the last trimester of gestation (60-90%). The frequency of transmission is inversely related to the severity of the disease (Remington, 2006). The clinical course in the infant or child is however not related to the presence or absence of symptoms of the disease in the mother.

Clinical manifestation of toxoplasmosis because of immunosuppression, typically due to reactivation of a chronic infection or acquisition of a new infection, manifests primarily as toxoplasmic encephalitis (TE) also known as central nervous system toxoplasmosis (Luft et al., 1983)(Luft et al., 1984). Disease progression leads to severe manifestations such as confusion, lethargy, mental state changes, seizures, and coma, and the outcome is fatal (Hill and Dubey, 2002). Approximately two thirds of all people currently living with HIV are found in the sub-Saharan region of Africa. According to UNAIDS 2008 report on the global AIDS epidemic, about 5.7 million South Africans were infected and living with HIV in 2007, with obvious risk and health resource implications for reactivation or acquisition of infections including toxoplasmosis (Kistiah et al., 2011).

In the pre-HAART era, toxoplasmic encephalitis was the leading cause of death in patients with AIDS worldwide and was known to occur in 3 to 40% of all patients with acquired immunodeficiency syndrome (Jones et al., 2003)(Jones and Dubey, 2012). However, fortunately with the onset and wider availability of HAART, morbidity, mortality and healthcare utilization related to *Toxoplasma* encephalitis has declined noticeably (Saadatnia and Golkar, 2012).

Focus has shifted recently to the growing population of infants born to HIV-positive mothers, but who themselves are HIV-negative (HEU). These infants, compared to their HIV unexposed, uninfected counterparts appear to be at increased risk of hospitalization due to serious infections (Slogrove et al., 2012). Especially those born to mothers who are infected simultaneously with HIV and *T. gondii* should be evaluated for congenital toxoplasmosis, as there is an increased risk of reactivation and disease particularly in the more severely immunocompromised mother.

There is limited literature on toxoplasmosis and tuberculosis co-infection. However, tuberculosis is a common co-infection of HIV and hence compounds the potential for cerebral toxoplasmosis. Toxoplasmosis together with toxocariasis and tuberculosis, are the most common causes of lymphadenitis in children (Guneratne et al., 2011). Hwang et al., recently reported the co-infection of tuberculosis and cerebral toxoplasmosis in an otherwise immunocompetent individual and they attribute the opportunistic toxoplasmosis infection to immunosuppression caused by the coexistent tuberculosis (Hwang et al., 2012).

### 2.1 Modification of Host Behavior

The dormant, latent or chronic form of human toxoplasmosis was thought to be asymptomatic during the latent period, however; recently the adverse effect of the supposedly latent infection on the infected individual's reaction time, tendency for accidents, behavior and mental illness has become a focus of research.

In animal studies, rodents that are chronically infected with toxoplasmosis lose their aversion to their felid predators and are attracted to their odor which results in more successful predation (Dass et al., 2011). Latent *T. gondii* infection may even have an effect on psychomotor performance as well as on personality profiles of infected humans, consistent with effects observed in the rodent models (Flegr and Hrdý, 1994)(Flegr, 2007)(Flegr, 2013).

Increased levels of anti *T. gondii* IgG antibody levels have been reported in schizophrenia patients at the onset of the disease and increased suicidal tendencies in latently infected human females, whilst latently infected males have been observed to become erratic or reckless in behavior (Fuks et al., 2012)(Carruthers and Suzuki, 2007).

Mothers infected with *T. gondii* were found to be more likely to indulge in self-directed violence (Pedersen et al., 2012). *T. gondii* infection has also been associated with bipolar disorder type 1 disease (Hamdani et al., 2012)(Pearce et al., 2012).

Fuks et al. 2012, proposed that the mechanism for this as being the invasion of dendritic cells and subsequent modification of gene expression in these cells to produce and secrete GABA, a well-known neurotransmitter (Fuks et al., 2012).

These observations give rise to speculations on the etiology of violence and the potential for intervention particularly for mental health disorders, the global and national burden of which is on the rise (Sorsdahl et al., 2011).

### 3. Prevalence of Human Toxoplasmosis in South Africa

Global *T. gondii* antibody sero-prevalence rates range from 0 to 100% (Dubey and Beattie, 1988). The first prevalence study from South Africa in 1974 reported a 37% positivity in the former Transvaal region, the highest sero-prevalence in this study was amongst Indians (58%), followed by coloreds (43%), whites (33%) and blacks 29% (Mason et al., 1974).

In 1978, national sero-prevalence of 20% was reported, on samples representing all provinces and ethnic groups (Jacobs and Mason, 1978). In 1992, Schneider, Schutte and Bommer, reported a sero-prevalence of 12.5% in whites, in coloreds 28.3%, 36.9% in Indians and 46.2% in blacks (Schneider et al., 1992).

Fielder et al. in 1995, reported sero-prevalence rates of 43% in blacks, 26% in colored and 15% in whites in 480 consecutive HIV infected individuals in the Western Cape (Fielder et al., 1995). Sonnenberg, Silber and Jentsch (1998), documented a sero-prevalence rate of 24.6 in black HIV (+) patients from the Eastern Cape and KwaZulu-Natal Provinces, Lesotho and Mozambique (Sonnenberg et al., 1998).

However, a study from the Gauteng Province by Hari *et al.*, in 2007 was of 307 black HIV infected in-patients who were not on antiretrovirals or receiving cotrimoxazole reported a sero-prevalence rate of only 8% (Hari et al., 2007).

Bessong and Mathomu (2010) reported a sero-prevalence of 18.1% in a retrospective study of *T. gondii* infection in HIV-positive individuals in Venda, north-eastern South Africa, but they noted that females between the ages of 21 to 35 had a sero-prevalence rate of 82% (Bessong and Mathomu, 2010). However, Kistiah *et al.*, 2011 reported a sero-prevalence of 9.8% amongst a cohort of HIV positive and negative patients and only 12.8% prevalence in a cohort of HIV positive pregnant women in Gauteng Province (Kistiah et al., 2011).

The above studies were not systematic; they focused on different populations and different diagnostic tests, making comparison difficult. Risk factors were not detailed and at-risk groups not monitored over time for clinical relevance. Extremely high seroprevalence rates 82% (north-eastern South Africa) were reported as well as low prevalence (8%, 9.8%) in the coastal surveys.

#### 4. Diagnostic and Treatment Challenges

The most commonly used initial laboratory test for diagnosis is the serological detection of specific IgG, IgM and IgA antibodies to *T. gondii* by commercially available test kits. Although IgM antibodies decline faster than IgG antibodies, they may persist at high levels for up to 18 months, making the diagnosis of congenital infection difficult. In this setting and where only a single sample is available the more recently available IgG avidity test may be helpful and assist in differentiating recent infection with low avidity (weak antigen binding) from chronic infection with high avidity IgG antibodies (strong antigen binding) to help rule out infections in the last 4 to 5 months. PCR diagnosis on amniotic fluid samples of gestations identified at risk serological or suggestive ultrasonographic features of the foetus have a reported specificity of close to 100% for *T. gondii*. Serologic methods for diagnosis in AIDS patients and the immune-compromised are unreliable due to deficient specific antibody production. Prevention strategies for infection with *T. gondii*, especially in pregnant females revolve around health education for personal hygiene and food handling (Bope and Kellerman. 2013).

Specific treatment of the immune-competent, non-pregnant patient is generally not indicated, as infection is usually subclinical and self-limited. For pregnant women (if infection is diagnosed) and the immune-compromised however, treatment with anti-toxoplasmic agents such as a combination of pyrimethamine, sulphonomides and spiramycin directly after diagnosis is indicated (Bope and Kellerman. 2013).

#### 5. Conclusions

Currently South Africa is burdened with ongoing HIV and TB pandemics. South Africa accounts for 17% of the global HIV burden and has a TB incidence of 950 per 100,000, as at 2012 (Mayosi and Benatar, 2014). Overall, reported seroprevalence rates in Africa are high in both human and animal populations. The likelihood of disease transmission via contaminated food and water sources in the HIV era has serious implications for underdeveloped countries, hence the increased risk of toxoplasmosis as a waterborne or food borne disease (Conrad et al., 2005). Toxoplasmosis presents a challenge in its diagnosis and treatment of recent infection and reactivation, as it requires a combination of tests which have to be interpreted in the context of clinical examination and history for appropriate intervention, especially in pregnancy and for the immune suppressed. A more systematic approach towards *Toxoplasma gondii* seroprevalence data gathering and analysis is called for in Africa, for effective approaches to prevention and disease reduction.

*T. gondii* has been neglected as a health risk to the general population in the HIV era and there is lack of accurate information on prevalence in human and animal populations and its importance in the food chain and in water sources. The emerging evidence concerning its potential effects on the mental health of infected but apparently physically healthy individuals should prompt further research.

Future work should also focus on the monitoring of sensitive populations such as pregnant women, cats (both feral and domestic), HIV and TB patients and small ruminants such as sheep. The molecular epidemiology of the pathogen also needs to be investigated in order to have an understanding of the strains that are causing infection in South Africa and where they fit in within the African as well as global phylogeny and also their virulence phenotypes.

Finally, there is the need to institute policies on advocacy and active surveillance of at risk populations in order to create adequate awareness and hence aid in prevention of any unexpected outbreaks.

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