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Toxoplasmosis: Overview from a One Health perspective

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ABSTRACT

Toxoplasmosis is paradigmatic of the One Health approach, as the causative parasite *Toxoplasma gondii* infects virtually all warm-blooded animals, including humans. This makes *T. gondii* one of the most successful parasites on earth, infecting up to a third of the global human population. Moreover, the *T. gondii* disease burden has been ranked among the highest of all parasitic diseases. To reduce the disease burden of toxoplasmosis in humans, interventions are needed in the animal reservoirs, necessitating close collaboration between both the human and veterinary medical sectors. In the present special issue of FAWPAR, several of the most pertinent topics related to the impact and control of toxoplasmosis are addressed by leading experts in the field. This collection of papers highlights state-of-the-art knowledge, gaps in knowledge and future perspectives, as well as the benefits of current and proposed future activities to tackle toxoplasmosis within the One Health context.

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With its omnipresence and wide array of hosts, including all warm-blooded animals and some cold-blooded animal species, *Toxoplasma gondii* may be the most successful parasite on earth, estimated to infect up to one third of the global human population (Montoya and Liesenfeld, 2004). The organism's life cycle is complex with a final sexual phase of reproduction in the intestines of members of the Felidae family (definitive hosts) resulting in the production of oocysts. Asexual reproduction of the parasite occurs in a broad range of intermediate hosts. In the intermediate host, *T. gondii* persists by conversion from the proliferative tachyzoite stage into quiescent encysted bradyzoites, a mechanism controlled by the host immune response. Thus, although generally mild and self-limiting in immunocompetent individuals, *T. gondii* infection may cause life-threatening disease in the fetus and in the immunosuppressed host.

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For almost 80 years, toxoplasmosis has been recognized as an important disease by both physicians and veterinarians. Veterinarians first became concerned by the severe economic losses in sheep flocks induced by the abortive potential of the parasite (Hartley and Marshall, 1957). Physicians were already aware of the occurrence of severe cases of congenital toxoplasmosis (Sabin, 1942; Couvreur and Desmonts, 1962). The development of the first serological test to examine individuals exposed to the parasite - the Sabin-Feldman test - allowed for the first epidemiological investigations of human infection in the late 1940's (Sabin and Feldman, 1948). The first prospective studies of pregnant women for toxoplasmosis in France and Austria (Thalhammer, 1973; Desmonts and Couvreur, 1974) led to the initiation of screening programs, and the development of therapeutic intervention strategies, including advocating for hygienic measures for the prevention of toxoplasmosis (Jeannel et al., 1990; Bénard et al., 2008). Timely detection of primary infections and subsequent intervention led to a decrease in the number of severe cases of congenital infection such as hydrocephalus, microcephalus or hydrops fetalis, and needless therapeutic abortions in women were drastically reduced (Ambroise-Thomas et al., 2001). However, even with such programs in place, and coupled with systematic fetal ultrasound monitoring, cases of congenital toxoplasmosis still do occur. These cases actually represent the bulk of the burden of disease caused by *T. gondii*, ranked among the highest of all foodborne parasitic diseases on the global level (Torgerson et al., 2015), the third among all food-borne pathogens in the US (Batz et al., 2012), and the second among food-borne parasites in Europe (Bouwknegt et al., 2018).

It has been a long road from recognizing congenital toxoplasmosis as the main clinical issue caused by *T. gondii* infection to today's debates on the association of *T. gondii* with chronic neurological and psychiatric conditions, particularly schizophrenia and bipolar disorder (Ngoungou et al., 2015; Fabiani et al., 2015; Fuglewicz et al., 2017). Interest in this topic has been instigated by observations that the parasite can modify the behavior of infected rodents to facilitate its transmission.

However, all this knowledge has not yet resulted in effective control of the parasite. Preventing human exposure by reducing *T. gondii* in animal reservoirs could be the optimal control measure and options for intervention strategies are being discussed (Opsteegh et al., 2015). The veterinary sector developed one of the first anti-parasite vaccines (Toxovax^{R}, MSD Animal Health) to prevent abortion in sheep flocks (Wilkins and O'Connell, 1983; Buxton et al., 1991), but there is still no vaccine to prevent toxoplasmosis in humans.

The introduction of amniocentesis and cordocentesis into routine clinical practice 30 years ago made it possible to achieve rapid prenatal diagnosis of fetal toxoplasmosis. The detection of viable *T. gondii* by bioassay in mice or by isolation in cell culture (Derouin et al., 1987) was soon replaced by the detection of the parasite DNA by PCR. The routine implementation of PCR enabled a parasitological diagnosis within a few days at that time (Burg et al., 1989; Grover et al., 1990), and currently, with real-time PCR, within a few hours. PCR-based techniques soon found application in the diagnosis of cerebral and disseminated toxoplasmosis, which had emerged as clinical issues with the advent of the devastating AIDS pandemic. The PCR has become an indispensable tool for the diagnosis of toxoplasmosis in all categories of immunosuppressed patients (Dupouy-Camet et al., 1993), including those with ocular toxoplasmosis (Montoya et al., 1999).

The ability to diagnose congenital cases in utero and disseminated forms in immunosuppressed patients underscores the limitations of the available treatment options. The rather small repertoire of effective drugs (pyrimethamine, sulfadiazine, sulfadoxine, clindamycin, spiramycin) is additionally limited by important side effects. Physicians need a better arsenal of parasiticidal drugs for the treatment of toxoplasmosis. Even though many new or re-purposed candidates have been screened, this has not yet resulted in novel drugs for routine use, particularly those active against the tissue cysts.

The in-vitro cultivation of *T. gondii* opened the door to phenotypic and genotypic analyses, which showed that the parasite is comprised of several clades characterized by different pathogenicity (Dardé, 1996). Isolation and genetic characterization of *T. gondii* strains from backyard chickens revealed that the South American *T. gondii* isolates were phenotypically (mouse virulent) and genetically (atypical) different from those in the rest of the world (Dubey et al., 2002; Lehmann et al., 2006). Unusual, atypical genotypes of *T. gondii* were shown to cause fatal acquired toxoplasmosis in non-immunosuppressed patients in French Guiana and Surinam (Carme et al., 2009; Demar et al., 2007). This was followed by significant development in the understanding of the genetic diversity of *T. gondii* at the global level and in a wide range of hosts, and the implications it may have on clinical disease.

Epidemiological surveys over decades of research have repeatedly showed extremely wide differences in the prevalence of *T. gondii* infection at the global level. In the 21st century, the prevalence ranges from below 1% in South Korea to as high as 77% in Brazil. Foci of high prevalence exist in South America, parts of Eastern/Central Europe, the Middle East, parts of south-east Asia and Africa (Pappas et al., 2009). Understanding the reasons underlying the variable prevalence rates found in even geographically close areas led to interest in the infection risk factors. Studies frequently showed that the main risk factor for humans was not the cat but the consumption of undercooked meat (pork, lamb, beef, horsemeat) and that local seroprevalence variations correlated with meat cooking preferences (Kapperud et al., 1996; Bobić et al., 1998; Cook et al., 2000). However, the recent development of a serologic test to distinguish oocyst- versus meat-induced infections revealed that the ingestion of oocysts is likely a more important source of infection than ingestion of undercooked infected meat, at least in the United States (Hill et al., 2011; Boyer et al., 2011). Needless to say, the relative significance of these two transmission routes (via oocysts or tissue cysts) is still unclear and needs to be clarified in order to select and prioritize the most appropriate options for effective control. Nevertheless, the fact that meat is one of the main transmission routes in many countries should urge the relevant veterinary authorities worldwide to implement suitable control methods to prevent human exposure to the parasite via relevant meat producing animals. This also calls for source attribution and risk assessment approaches to garner knowledge of the most important meat and meat product sources as has been described for the Netherlands (Opsteegh et al., 2011) and Italy (Belluco et al., 2018). Reduction of human exposure can currently be achieved via the control of *T. gondii* in primary production systems by improving biosecurity, identifying and removing infected food animals from the food chain, or the physical destruction of the parasites in meat, by freezing (Dubey et al.,

1990), cooking (Kotula et al., 1991), addition of salts (Hill et al., 2006), and use of validated curing methods (Hill et al., 2018; Fredericks et al., 2019). Effective vaccination of animals to reduce the formation of tissue cysts in meat is the ideal approach. Although a live attenuated vaccine has proven its efficacy in reducing abortion in sheep flocks, and other vaccines were able to reduce the parasitic burden, none can eliminate the parasite. However, any reduction in the number of *T. gondii* tissues cysts in pork and lamb should improve food safety, as recently shown (Burrells et al., 2015; Katzer et al., 2014). Another approach would be to vaccinate the definitive host but such a strategy would not mitigate infection in feral and free-ranging cats, which are important reservoirs of *T. gondii* (Suijkerbuijk et al., 2018).

In this special issue devoted to toxoplasmosis in the One Health context, a range of topics dealing with its impact and control is discussed. Bobić, Villena and Stillwaggon review the benefits and economic costs of different prevention programs for congenital toxoplasmosis (Bobić et al., 2019 - this SI). National screening programs implemented in France and Austria are described, and the feasibility and cost-effectiveness of implementing such nation-wide screening in low-prevalence countries such as the United States is analyzed. In addition, the authors discuss new diagnostic tools and the implications of their lower costs both in settings with established screening programs and in those with inadequate prenatal care systems.

Dardé and her group draw from their 25-year long experience in genotyping *T. gondii* strains (Galal et al., 2019 - this SI). They review the parasite population structure in light of the main dichotomies observed, including those in domestic versus wild animals, in South America versus the rest of the world, and in intercontinental versus regional/local clonal lineages, and the impact of such a genetic diversity and its determinants on public health. Moreover, the authors discuss new challenges in the One Health context posed by a rapid evolution of the *T. gondii* population spatial structure driven by global trade and movement of animals.

Schares assembled a group of experts to provide a comprehensive review on *T. gondii* infection in farm animals, summarizing current knowledge on the prevalence of and potential risk factors for *T. gondii* infection in the most important livestock species (Stelzer et al., 2019 – this SI). They also identify knowledge gaps in this field, which mostly involve lack of data on the costs associated with *T. gondii* infection in livestock production.

Another group of experts led by Shapiro review the critical role of *T. gondii* oocyst for the parasite's success, focusing on aspects ranging from dynamics of oocyst excretion by felids to the occurrence and transmission patterns of oocysts in soil, water and foods (Shapiro et al., 2019 – this SI). They discuss critical control points for reducing the risk of exposure to oocysts, and identify gaps in current knowledge for mitigating the risk of oocyst-acquired toxoplasmosis in humans, domestic animals, and wildlife.

Innes and colleagues review the current standing of vaccines against *T. gondii* (Innes et al., 2019 – this SI). The authors discuss a One Health approach to develop a vaccination program against *T. gondii* infection and/or toxoplasmosis, with the goals of preventing or reducing a) congenital disease in humans (and sheep), b) tissue cysts in food animal species, and c) oocyst excretion in cats. As the tools and technologies are now available, the authors conclude it is time to make it happen.

Lastly, Robert-Gangneux and coworkers discuss the current therapeutic approaches to the main disease entities caused by *T. gondii*; unfortunately, these regimens have not changed much in the last decades due to the lack of progress in developing new chemotherapeutic agents (Konstantinović et al., 2019 – this SI). Regardless, future prospects are discussed in light of ongoing research on both new drugs and immunotherapeutic strategies.

The articles in this special issue provide an overview of current knowledge on the impact and control of infection by an organism discovered more than a hundred years ago (Nicolle and Manceaux, 1908), but which still presents a global public health challenge. It is increasingly evident that the control of *T. gondii* can only be achieved through the concerted efforts of the medical and veterinary sectors, thus making it a paradigmatic example of the One Health concept.

Conflict of interest statement

The authors declare they have no conflicts of interest whatsoever.

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