Food and Waterborne Parasitology 22 (2021) e00102

Contents lists available at ScienceDirect

Food and Waterborne Parasitology

journal homepage: www.elsevier.com/locate/fawpar

Mathematical modelling of *Toxoplasma gondii* transmission: A systematic review

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ARTICLE INFO

Article history:
Received 1 July 2020
Received in revised form 27 November 2020
Accepted 4 December 2020

Keywords:
Zoonoses
Mathematical model
Toxoplasmosis
Transmission
Modelling

ABSTRACT

Background: *Toxoplasma gondii* is a ubiquitous protozoan parasite that can infect virtually all warm-blooded animals. It is the causative agent of toxoplasmosis, a significant public health issue worldwide. Mathematical models are useful to study the transmission dynamics of *T. gondii* infection in different settings, and may be used to compare the effectiveness of prevention measures.

Methods: To obtain an overview of existing mathematical models for transmission of *T. gondii*, a systematic review was undertaken. The review was conducted according to an a priori protocol and the results were reported according to the PRISMA guidelines. Specific search terms were developed and used in the search of three databases (Scopus, PubMed, and Embase).

Results: In total, 484 unique records were retrieved from the systematic search. Among them, 15 studies that used mathematical models to study the transmission of *T. gondii*. These studies were categorized into four groups based on the primary aims: dynamics of transmission ($n = 8$), intervention ($n = 5$), spatial distribution ($n = 1$), and outbreak investigation (n = 1).

Conclusions: Considering the high disease burden caused by *T. gondii*, the number of studies using mathematical models to understand the transmission dynamics of this parasite and to evaluate the effectiveness of intervention measures was only 15. This systematic review provides an overview of existing mathematical models and identifies the data gaps for model building. The results from this study can be helpful for further development of mathematical models and improved understanding of the transmission dynamics of *T. gondii* infection.

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https://doi.org/10.1016/j.fawpar.2020.e00102

Contents

1. Introduction

Toxoplasma gondii is one of the most widespread zoonotic parasites in the world, that can infect virtually all warm-blooded vertebrates. *T. gondii* is the causative agent of toxoplasmosis, a potentially serious disease in humans leading to a large public health burden and causing large economic losses in the livestock industry due to abortion and stillbirth (Tenter et al., 2000).

T. gondii has a complex life cycle functioning in a prey-predator system (Fig. 1). It involves three infectious stages (invasive tachyzoites rapidly dividing and spreading in nucleated cells, slowly dividing bradyzoites in tissue cysts, and sporozoites in oocysts), sexual and asexual reproduction, and multiple hosts (Dubey, 1998). As the only definitive host of the parasite, members of the felidae family play the most important role in *T. gondii* transmission. Cats can become infected by ingesting any of the three infectious stages of *T. gondii* (Miller et al., 1972), and following sexual reproduction in their intestines they can excrete millions of unsporulated oocysts into the environment through faeces (Dubey et al., 1970). This may continue for up to about 20 days (Dubey, 1995). Oocysts sporulate within a few days in the environment and can remain infectious for more than a year in soil or water under ambient conditions. A wide range of warm-blooded animals can get infected by ingestion of sporulated oocysts from contaminated environments and serve as the intermediate hosts of the parasite (Dubey, 1998). After ingestion of oocysts by an intermediate host, sporozoites are liberated in the intestine of the host where they invade enterocytes and differentiate into tachyzoites. Tachyzoites are disseminated rapidly via the blood stream to all tissues, and are able to infect all nucleated cells. Immune pressure triggers the conversion of tachyzoites into bradyzoites in tissue cysts, which form 7–10 days after infection and remain viable in multiple organs, including the central nervous system tissue and muscles (including the heart). It is generally believed that cysts may remain viable for the life of the host, triggering life-long immunity, but this concept has recently been challenged (Rougier et al., 2017). If a definitive host ingests an infected intermediate host (e.g., rodents or birds), then the cycle of *T. gondii* is completed. Moreover, *T. gondii* can be transmitted between intermediate hosts via carnivory, e.g., when people consume undercooked meat containing tissue cysts (Robert-Gangneux and Darde, 2012). In addition, *T. gondii* may be transmitted vertically; if primary infection occurs during pregnancy, the tachyzoites can cross the placenta and infect the fetus, leading to congenital toxoplasmosis (CT) (Dunn et al., 1999).

The bulk of the recognized burden of disease associated with human *T. gondii* infection is actually due to CT. In 2013, the annual global incidence of CT was estimated at 1.5 cases per 1000 live births, and the burden of CT was estimated to be 1.2 million DALYs (95% CI: 0.76–1.90) (Torgerson and Mastroiacovo, 2013). At the European level, *T. gondii* ranked second out of 24 foodborne parasites in a multicriteria-based ranking which considered public health, trade, and socio-economic impact (Bouwknegt et al., 2018). Despite the high disease burden of *T. gondii* infection at both the population and individual level, toxoplasmosis is considered a neglected parasitic infection in the United States (Jones et al., 2014). In Europe, only a few countries (Austria, Belgium, France, Portugal, Slovakia and Slovenia) have active surveillance of congenital cases by mandatory screening of pregnant women, which show that relatively little attention has been devoted to its surveillance, prevention and treatment (DGS, 2013; ECDC, 2019; Peyron et al., 2017). Several intervention strategies have been proposed to reduce the disease burden of human infection, such as prenatal/neonatal screening and treatment, health education of pregnant women/general population, freezing of meat destined for raw or undercooked consumption, vaccination of cats, and biosecurity measures for food animals (Opsteegh et al., 2015). However, except for health education and screening of pregnant women and other risk groups, additional intervention measures targeting the sources of infection are generally not in place because it is difficult to evaluate the balance between costs and benefits (Binquet et al., 2019; Bobić et al., 2019; Stillwaggon et al., 2011).

Models use mathematical language to describe the behavior of a system and are useful to study the transmission dynamics of infectious diseases in different settings. They help better understand the transmission of a pathogen and can be used to validate, compare and optimise the preventive measures. For example, compartment models, where the total population is divided into different compartments, are widely used in epidemiological studies to investigate the spread of infectious disease at the population level (Brauer et al., 2008). A simple and widely used compartment model is the SIR model, which consists of three

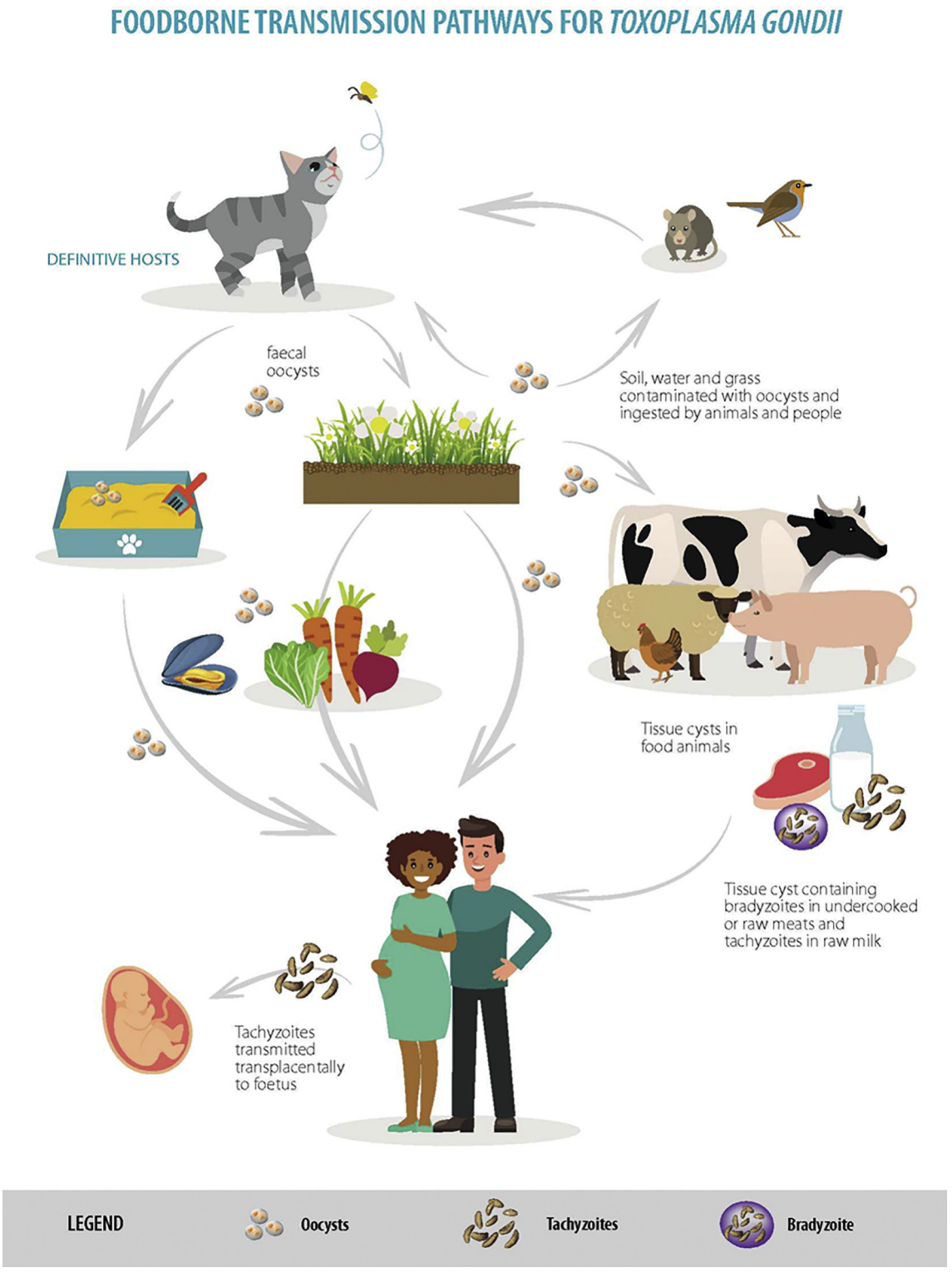

Fig. 1. Life cycle of *Toxoplasma gondii*, adapted from EFSA BIOHAZ Panel (2018).

sub-populations, representing the number of susceptible (S), infected (I) and recovered (R) individuals in each compartment at a particular time. The mathematical quantity of major interest is the basic reproduction number (R_0), i.e., the average number of secondary cases generated by a typical infected individual introduced into a completely susceptible population (Dietz, 1993).

Typically, its value determines whether an infectious disease can spread through a population or not. If R_0 is less than one, the disease will eventually die out, i.e., the population reaches a disease-free equilibrium. On the other hand, if the basic reproduction number is larger than one, the disease will be able to spread and remain in the population. However, *T. gondii* is not only transmitted between definitive hosts, but can also be transmitted via intermediate hosts and has a reservoir in the environment. Therefore, an SIR-model does not capture all compartments important in the transmission of *T. gondii* infection. Moreover, although cats excrete oocysts temporarily and move from the I to the R compartment regarding oocyst excretion, both cats and intermediate hosts will harbour tissue cysts potentially for life and remain infectious via carnivory, therefore an R compartment is not applicable for the tissue cyst route.

The aim of this study was to provide an overview of existing mathematical models on the transmission of *T. gondii* between different compartments (e.g., felines, environment, intermediate hosts, mechanical vectors) and analyse model structures and outcomes by performing a systematic review. In addition to a comparison of the models, we also aimed to describe and compare the prevention and control strategies investigated by the models.

2. Methods

2.1. Search strategy

A systematic review following a predefined protocol was performed and reported based on PRISMA guidelines (www.prisma-statement.org). A search for eligible studies was carried out using three bibliographic databases: Scopus, PubMed, and Embase. For the initial identification of relevant studies we considered the development of specific search terms on the following key subjects: (1) *T. gondii* is the pathogen of interest; (2) it includes mathematical models; (3) the underlying model to the study of *T. gondii* transmission is mechanistic in its approach; (4) transmission of *T. gondii* between any of the compartments (i.e., feline definitive host, animal intermediate hosts (prey animals or livestock/wildlife for human consumption), humans, environment (e.g., soil and water), oocyst-contaminated produce or shellfish, and mechanical vectors (e.g., flies and worms)) or climatic conditions that influence oocyst dispersion and survival is described.

The databases were searched using keywords (with the use of Medical Subject Heading (MeSH) or Emtree terms used in PubMed and Embase respectively) associated with the Boolean operators AND/OR. Different combinations were tailored for each database in order to narrow the number of results retrieved but at the same time maximizing the number of relevant studies. The search language was restricted to English. There were no restrictions in study year or geographical location. Grey literature was not searched for. Retrieved records were imported in EndNote and duplicates were removed. The search strategy was validated for reliability, using a subset of publications already identified as relevant to the objective (Table 1). The final search (Table 2) was performed on January 13th, 2020.

2.2. Selection criteria

Studies retrieved from the databases were assessed against the inclusion and exclusion criteria for relevance and eligibility. Before examination of all retrieved papers, publications indexed as review or letter to editor (i.e., no original research papers) were excluded by two researchers (pre-title/abstract screening), and all the remaining publications were assigned to all researchers for screening. The screening was performed in two stages. First, a title and abstract screening was performed for relevance. The inclusion criteria for this stage were paraphrased into the following questions: (1) is an abstract available? (yes/no); (2) is *T. gondii* studied in the publication? (yes/no/unclear-full text required); (3) does the title/abstract suggest that a mathematical model is used to study transmission? (yes/no/unclear-full text required). All unique records were divided among all researchers, and were assessed by two different researchers at both title/abstract stage and full text stage. A third reviewer was consulted if a publication had contradicting results. If the first reviewer considered a record relevant or unclear, it was included in the full-text screening, and if the record was not considered relevant, it was screened by the second reviewer. If the second reviewer considered the record relevant or unclear it was included in the full-text screening, if the second reviewer agreed that the record was not relevant, the record was placed in the list of non-relevant records. If no abstract was available or any of the inclusion criteria mentioned above could not be properly evaluated based on title and abstract alone, the eligibility of those studies was evaluated based on the full text. Second, a full-text screening was performed on the publications selected in the first stage. Additional exclusion criteria applied in this phase included: (1) full-text could not be obtained within two weeks after the selection for full-text screening was completed for all records; (2) publication contains only duplicated data; (3) purely descriptive or statistical models that seek to fit data without consideration of underlying biological mechanisms (e.g., risk factor analysis); (4) mother to child transmission; (5) quantitative microbial risk assessment studies (they were included in another systematic review concerning source attribution of *T. gondii* infection). The screening was performed using Epi Info (CDC, version 7.1.5). A PRISMA flowchart was used to summarize all stages of the paper selection process.

2.3. Data extraction

Data were extracted from all eligible papers using a predefined electronic form containing the following components: (1) the characteristics of the included studies (reference, published year, title); (2) location (where the study population was located); (3) model objectives (e.g., dynamics of transmission and evaluation of intervention strategies); (4) transmission routes

Table 1
Articles used to validate the search query.

References	DOI
Arenas et al., 2010	https://doi.org/10.1016/j.tpb.2010.03.005
González-Parra et al., 2009	https://doi.org/10.1016/j.camwa.2008.09.012
Gotteland et al., 2014b	https://doi.org/10.1186/1476-072X-13-45
Jiang et al., 2012	https://doi.org/10.1016/j.jtbi.2011.10.006
Lélu et al., 2010	https://doi.org/10.1016/j.tpb.2010.05.005
Turner et al., 2013	https://doi.org/10.1016/j.tpb.2013.04.001

of *T. gondii*; (5) model setting (e.g., urban and farm); (6) type of model (e.g., compartment model and agent-based model); (7) model outputs (e.g., environmental contamination rate, *T. gondii* prevalence, and R_0).

3. Results

The systematic search provided 484 records. All articles already identified as relevant to the objective a priori (Table 1) were also retrieved in the final search strategy. Forty-eight of the available records did not fit the inclusion criteria and were excluded based on title before title and abstract screening. The entire list of 436 records can be found in the supplementary material A. After the title and abstract screening, 63 studies were selected for full-text screening. Of the 63 studies, 15 met the inclusion criteria after full-text screening and were included in the systematic review (Fig. 2). A PRISMA checklist can be found in the supplementary material B.

All included studies were published between 2002 and 2020, except one, which was published in 1982. Results were presented in four different categories: dynamics of transmission ($n = 8$), intervention ($n = 5$), spatial distribution ($n = 1$) and outbreak investigation ($n = 1$) (Table 3). One paper that fit more than one category (the spatial distribution and the dynamics of transmission categories) was only included in the spatial distribution category.

3.1. Dynamics of transmission

Of the selected papers, eight were classified as transmission dynamic modelling. These models were compared based on the compartments that were incorporated in the models (e.g., cats, mice, humans and environment).

3.1.1. Cat-human transmission

Three papers focused on cat-human transmission (Ferreira et al., 2017; González-Parra et al., 2009; Yongzhen et al., 2018). González-Parra et al. (2009) developed a compartment model for exploring the dynamics of *T. gondii* transmission to humans (SIC-type: susceptible, infected, controlled (people in treatment)) with cat (SI-type: susceptible, infected) as a vector of transmission. These two populations were linked with the assumption that both humans and cats get infected with *T. gondii* only through contact with infected cats. In the model, the human and feline population sizes were set as constant by assuming birth rate equal to death rate. Vertical transmission in both populations was considered in the proposed system. In the human population, vertical transmission was assumed with a probability of one, whereas a cat born from an infected cat had a probability p_c of not being infected. Scenario analysis concerning the R_0 and vertical transmission of *T. gondii* in cats revealed that the R_0 in cats completely controlled the dynamics of the infection and when a high vertical transmission in a cat population was assumed, the endemic equilibrium point had a higher proportion of infected cats and infected humans at the steady state.

Ferreira et al. (2017) and Yongzhen et al. (2018) extended the model of González-Parra et al. (2009) to describe the transmission of *T. gondii* between cat and human populations. Both models assumed that horizontal transmission of the parasite to humans and cats was only through contact with infected cats. Ferreira et al. (2017) extended the model with a spatial version and similar to González-Parra et al. (2009), they showed that the R_0 depends on the contact rate of susceptible cats with infected cats, the birth/immigration rate of cats and the probability of effective infectious contact among cats. In the study by Yongzhen et al. (2018), vertical transmission was considered (both cats and humans born from an infected mother had probabilities (p_1 and p_2) of not being infected), and the human population size was a variable. They showed that whether the disease will die out or become endemic depends on cats' epidemiology parameters (e.g., birth rate, horizontal and vertical transmission). However, the underlying assumption that infected cats remain infectious for life is not realistic.

Table 2
Summary of the search results and search queries used for the systematic search, performed on January 13th, 2020.

Database	Number of retrieved records	Query
Scopus	433	(TITLE-ABS-KEY (*toxoplasmosis*) AND TITLE-ABS-KEY (*model*) AND LANGUAGE (*english*) AND TITLE-ABS-KEY (*mathematical* OR *transmission*))
Pubmed	144	(((toxoplasmosis) AND (transmission OR mathematical)) AND model) AND English[Language]
Embase	330	toxoplasmosis AND model AND (transmission OR mathematical) AND 'english':la
Total	907	

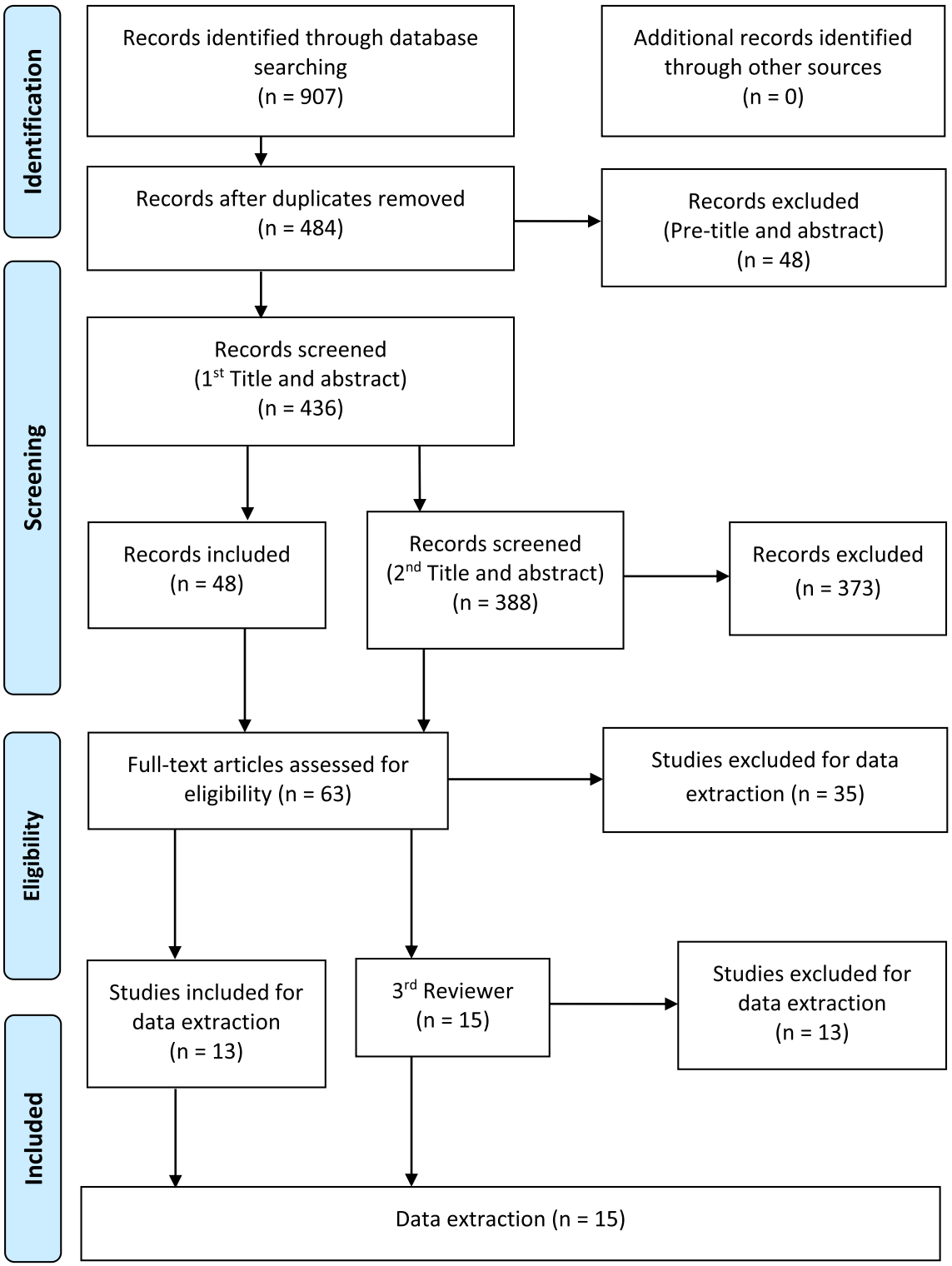

Fig. 2. PRISMA flow diagram: search steps and selection of relevant studies on mathematical modelling of *Toxoplasma gondii* transmission.

3.1.2. Cat-environment transmission

Most models selected studied the transmission of *T. gondii* between susceptible and infected hosts at population level. However, questions like how the transmission of disease among individuals is influenced by the within-host dynamics cannot be

Table 3
Summary of the 15 models identified by the systematic search.

Reference	Transmission route	Type of model	Role of stochasticity	Purposes of the study
González-Parra et al. (2009)	Cat-human	Compartment model	Deterministic	Dynamics of transmission
Ferreira et al. (2017)	Cat-human	Compartment model	Deterministic	Dynamics of transmission
Yongzhen et al. (2018)	Cat-human	Compartment model	Deterministic	Dynamics of transmission
Feng et al. (2013)	Cat-environment	Compartment model	Deterministic	Dynamics of transmission
Cen et al. (2014)	Cat-environment	Compartment model	Deterministic	Dynamics of transmission
Lélu et al. (2010)	Cat-environment-mouse	Compartment model	Deterministic	Dynamics of transmission
Lélu et al. (2013)	Cat-environment-mouse	Compartment model	Deterministic	Dynamics of transmission
Jiang et al. (2012)	Cat-environment-mouse	Agent-based model	Stochastic	Dynamics of transmission
Mateus-Pinilla et al. (2002)	Cats-finishing pigs-environment	Compartment model	Deterministic	Intervention-cat vaccination
Arenas et al. (2010)	Cats-environment	Compartment model	Deterministic	Intervention-cat vaccination
Turner et al. (2013)	Cat-environment-mouse-sheep	Compartment model	Deterministic	Intervention-cat vaccination and mouse elimination
Sykes (2015)	Cats-environment	Compartment model/ game theory	Deterministic	Intervention-cat vaccination
Bonačić Marinović et al. (2019)	Cat-environment-mouse-human	Compartment model	Deterministic	Intervention-cat vaccination
Gotteland et al. (2014b)	Cat-environment-mouse	Agent-based model	Stochastic	Spatial distribution
Shonkwiler and Thompson (1982)	Environment-human	Common source epidemic model	Stochastic	Outbreak investigation

answered using those models. The model by Feng et al. (2013) is the first to link between-host and within-host systems for studying the dynamics of *T. gondii* transmission, through their connection to a contaminated environment. However, also according to the authors, their model did not entirely reflect the complexity of the *T. gondii* life-cycle (Feng et al., 2013). In that study, an SI-type of model was used to describe the between-host dynamics of *T. gondii* in cats, and cats were assumed to acquire the infection only by ingesting oocyst contaminated food from the environment (which is not an important route of infection for cats (Dubey, 2010)). For the within-host dynamics, three compartments were considered in the system: density of uninfected cells, infected cells and parasite load. This study showed that the R_0 from the between-host system, within-host system and the coupled system determine the stability of the infection-free and the endemic equilibrium points. However, a possibility of a backward bifurcation for the coupled system was mentioned in Feng et al. (2013). Backward bifurcation is the phenomenon in disease transmission models where a stable endemic equilibrium co-exists with a stable disease-free equilibrium when the R_0 is less than one.

Cen et al. (2014) further analyzed the model proposed by Feng et al. (2013), and confirmed that backward bifurcation occurred in the model. The implication of backward bifurcation is that the requirement of R_0 being less than one is necessary but not always sufficient for disease elimination, making effective control difficult. The reader is referred to Dushoff et al. (1998) and Gumel (2012) for more details about backward bifurcation.

3.1.3. Cat-environment-mouse

The above models focused on the cat-human transmission route and cat-environment transmission route, but they neglected the intermediate host compartment (e.g., prey animals for felines or livestock/wildlife for human consumption) by either assuming that humans get infected by *T. gondii* through contact with cats or cats get infected through contaminated environment. However, epidemiological studies conducted in Europe have shown that humans mainly become infected via consumption of meat (Bobić et al., 1998; Cook et al., 2000), and cats may get infected from oocysts in the environment but with a much lower probability than from tissue cysts in prey (Dubey, 2010). Three studies concerning the transmission dynamics of *T. gondii* included mice in their models (Jiang et al., 2012; Lélu et al., 2010; Lélu et al., 2013). Lélu et al. (2010) developed a deterministic SIR-type model in which both definitive hosts (cats) and intermediate hosts (mice) were represented in the transmission cycle. In their model, cats become infected through contact with contaminated environment or by ingesting infected prey. They also assumed that cats defecate only in some areas of their habitat. Additionally, decontamination of the environment was considered. They concluded that a threshold of predation rate, depending on the size of the cat population, determines the dynamics of *T. gondii* transmission. When considering a population of 100 cats, if the predation rate is above the threshold of 9 prey/cat/year, the complex life cycle (*T. gondii* transmitted to a definitive host via predation of infected intermediate hosts) contributed most in spreading *T. gondii* infection. In contrast, if below the threshold, the spread of infection is predominantly transmitted via a simple life cycle (*T. gondii* transmitted to definitive hosts via contaminated environment). However, vertical transmission was neglected in both cat and prey populations. Although vertical transmission generally only occurs during the acute stage of infection, mice may transmit vertically in subsequent pregnancies (Owen and Trees, 1998).

Based on the same model structure used in 2010 (Lélu et al., 2010), Lélu et al. (2013) further investigated how parasitic manipulation of intermediate host behavior (assumed to increase the predation of infected rodents by definitive hosts), vertical transmission and virulence of strains affect *T. gondii* transmission and their effects on the R_0. They showed that manipulation is particularly advantageous for virulent strains and in epidemic situations, and the level of manipulation will evolve depending on the sex of the intermediate hosts and the transmission route. In another transmission model including cats, mice and the environment, Jiang et al. (2012) built an agent-based model to explore the transmission process of *T. gondii* in a farm setting and to investigate the impact of oocyst survival and seasonality on cat and rodent seroprevalence. In this model, primary infection and

secondary infection of cats were taken into account. The results showed that: (1) most cats are infected through preying on infected mice, while mice are mainly infected through vertical transmission; (2) reducing the number of mice on a farm can lead to eradication of the parasite; (3) intermediate virulent lineages can sustain the disease most efficiently.

3.2. Intervention

Of the selected papers, five implemented potential intervention strategies in the transmission model. Mateus-Pinilla et al. (2002) developed the first compartment model for *T. gondii* transmission in a swine farm setting. The model included three compartments: cats, finishing pigs and environment. Subsequently, the effect of vaccinating cats on the prevalence of *T. gondii* in finishing pigs was evaluated. In addition, the values of several model parameters were varied for testing the effects on *T. gondii* prevalence in finishing pigs. The authors found that a decrease in the initial number of cats on the farm and decreased oocyst survival impacted the prevalence more than vaccinating the cats. Arenas et al. (2010) investigated the transmission of *T. gondii* between cats and the environment (oocysts) under a continuous vaccination schedule for cats. Similar to the results obtained by González-Parra et al. (2009), they also found that the R_0 completely determines the dynamics of the infection. In contrast to the results by Mateus-Pinilla et al. (2002), Arenas et al. (2010) found that continuous vaccination of cats was more effective than removing the oocysts from the environment according to scenario analysis, and a low vaccination rate (0.1) was enough to reduce the R_0 to less than one. Turner et al. (2013) extended the model of Lélu et al. (2010) by taking the virulence of *T. gondii*, vertical transmission, and manipulation of host behavior (predation rate) into account. They investigated the effect of two intervention strategies (cat vaccination program and mouse elimination program) on *T. gondii* transmission and extended the model with an end receiver host, namely sheep. They demonstrated that infection can theoretically be controlled by implementing both control programs in the cat-mouse-environment system. However, the level of vaccination and/or elimination may not always be achievable. In a setting with 50 cats and 300 mice, the model estimated that approximately five years were needed to reduce the number of infected mice to close to zero when implementing the cat vaccination (vaccination rate: 3 $week^{-1}$) and the mouse elimination program (elimination rate: 0.8/52 $week^{-1}$) together (Turner et al., 2013). They also suggested that it is necessary to control the spread of infection in cats and mice in order to control the spread of infection in the end receivers. By taking the cost of vaccine and infection into account, Sykes (2015) used the transmission model from Arenas et al. (2010) to determine at what cost the cat owners are willing to vaccinate their pets. They found that there is a critical cost threshold above which no one will use the vaccine, whereas a high usage of vaccine could be achieved if the cost is slightly below the threshold. To evaluate the vaccination strategy, they used a payoff value to evaluate the vaccination strategy, which is the benefit an individual derives from implementing the strategy minus the cost of implementing such a strategy. However, the model neglected the infection of cats via prey animals and assumed that the cat owners become infected only via their infected cats. This may lead to an incorrect estimate of the risk of human infection, and subsequently of the cost of infection. Based on the model structure from Lélu et al. (2010), Bonačić Marinović et al. (2019) developed a compartment model and a dose-response relation upon oocyst ingestion to study the effect of cat vaccination in reducing the risk of human *T. gondii* infection. In addition, two modelling approaches regarding how human *T. gondii* infection take places via the contaminated environment were conducted. One approach considered a fixed probability of infection, and the other considered the probability of infection to be proportional to the oocyst abundance. These two approaches can be interpreted as if oocysts are clustered or homogeneously distributed in the environment, respectively. Similar to the finding by Turner et al. (2013), Bonačić Marinović et al. (2019) concluded that a high cat vaccination coverage was needed to reduce the number of human infections, and a high coverage was considered unfeasible for large cat populations.

3.3. Spatial distribution and outbreak investigation

Among all included publications, only one studied how landscape structures impact on the spatial distribution of *T. gondii* prevalence in cats and rodents as well as contamination in the environment (Gotteland et al., 2014b). The authors extended the agent-based model developed by Jiang et al. (2012) to describe the transmission dynamics of *T. gondii* and investigated the spatial distribution of *T. gondii* in the environment. In addition, the prevalence of *T. gondii* in cats and mice, and the soil contamination rate predicted by the model were compared to field data from the same study site for validation purposes. They showed that the relationships between the level of soil contamination and the distance to the nearest farm, and between level of soil contamination and the distance to the village center were similar. The model outcomes were also used to produce a risk map of *T. gondii* contamination in the environment.

One of the selected studies investigated an outbreak of toxoplasmosis among those who visited a riding stable in Atlanta, Georgia, in 1977 (Shonkwiler and Thompson, 1982). The authors used detailed data from individuals who visited the stable (e.g., location, frequency of visits, distance to oocysts and the estimated onset of illness) to predict the epidemic curves and probability of infection.

4. Discussion

Mathematical models may be useful tools for studying the transmission of *T. gondii* and evaluating potential intervention strategies, however our knowledge and information on how to develop/apply reliable models and interpret the model results are limited. Our systematic review found that only 15 mathematical models were published in the past decades for studying the

transmission dynamics and evaluating intervention strategies of *T. gondii*. Studies of other pathogens found a total number of 388 (Reiner Jr. et al., 2013) and 29 (Dixon et al., 2019) mathematical models concerning mosquito-borne pathogen transmission and *Taenia solium* transmission, respectively. The limited number of *T. gondii* mathematical models may largely be due to the complicated life cycle of the parasite, i.e., multiple hosts and different transmission pathways, which makes it very difficult to model. Thus, models do not always represent reality, for example, the models by González-Parra et al. (2009), Ferreira et al. (2017) and Yongzhen et al. (2018) did not include transmission via intermediate hosts (i.e., infection of cats via infected prey, and infection of humans via undercooked or raw meat containing tissue cysts), and have the underlying assumption that vertically infected cats excrete oocysts and infected cats remain infectious for life (i.e., infectious for humans and cats via contact), and the model did not differentiate between the sex of the cats, thus all infected cats were assumed to produce infected offspring at a varying probability. It is questionable whether the conclusions from these models have value in spite of these important omissions compared to current knowledge on *T. gondii* transmission.

Toxoplasmosis is considered a major cause of production losses in the small ruminant industry (Stelzer et al., 2019) and is a significant public health problem (Weiss and Dubey, 2009). For these reasons *T. gondii* epidemiology needs to be studied and toxoplasmosis prevented, and mathematical modelling may help. However, the complicated life cycle of *T. gondii* makes it difficult to choose a modelling approach that is simple but still captures all important aspects. We found that the most common modelling approach for studying *T. gondii* transmission was a deterministic, equation-based compartment model, but simulation-based agent-based models, a game theory model and a common source epidemic stochastic model were also used. Compartment models and agent-based models are two common frameworks for modelling infectious diseases. For compartment models, Anderson and May (1992) identified the two most important assumptions: homogeneity and law of mass action. The first one assumes that all individuals in a particular compartment behave in the same manner. The second one means that the rate of change of individuals in a compartment at the next time step is proportional to the number of individuals in the compartment at the current time step. In contrast, agent-based models are a step away from the homogeneity of compartment models, and they are used to simulate autonomous agents and their interactions within a constrained environment over time (Epstein, 2007). Agent-based models have been used for prediction, inference, and the study of hypothetical intervention strategies in the epidemiology field. However, they are often more complicated and require more computation time than compartment models. In the agent-based model developed by Jiang et al. (2012), the complete life cycle of *T. gondii* in a farm setting was considered. Gotteland et al. (2014b) further studied the transmission of *T. gondii* and spatial distribution of oocysts based on the model from Jiang et al. (2012), and obtained results that appear realistic in comparison to data observed in a field study (Afonso et al., 2009; Gotteland et al., 2013; Gotteland et al., 2014b). An advantage of this agent-based model was that the agents in the model (in this case cats and mice) were both autonomous and characterized by their own rules, and it included a detailed description of *T. gondii* transmission. Thus, the structure of this model may be used as a baseline for studying the transmission of *T. gondii* and evaluating potential control strategies. Moreover, it can be further extended by including other intermediate hosts, like farm animals and humans.

From the selected publications, most modelling work has focused on the epidemiological interaction between hosts and the proliferation dynamics within the hosts separately. To date, more studies have revealed new and interesting insights for disease dynamics by using linked between-host and within-host models (Gilchrist and Coombs, 2006; Qesmi et al., 2015). A recent systematic review has identified 24 papers across 30 years that include the linked models for different pathogens (Childs et al., 2019). Feng et al. (2013) published the first mathematical model coupling between-host and within-host dynamics of *T. gondii* infection. Cen et al. (2014) further analyzed this coupled model and proved that backward bifurcation can occur in the model. This finding can have important public health implications for controlling *T. gondii* infection, although, as the authors acknowledged, the model neglected the prey-predator (rodent-cat) interaction in the transmission process which may have influenced the results. They suggested that the model is more appropriate for an environmental-driven infectious disease with a simpler life cycle than *T. gondii*.

Our systematic review showed that the two main intervention measures examined in the mathematical models, included cat vaccination and mouse elimination. However, the efficiencies of these intervention measures were difficult to compare, as they were evaluated in models based on different structures and parameter values. A hypothetical perfect vaccine is often assumed in the analysis. Currently, there is no vaccine to prevent oocyst excretion by cats on the market. Experimentally, a chemically-induced mutant strain (T-263) has been shown to be effective (Frenkel et al., 1991), and more recently progress has been made with a HAP2 KO strain engineered with CRISPR/Cas9 technology (Ramakrishnan et al., 2019). Vaccine efficacy should be considered in future models. In addition to the need for tools to better evaluate the efficiency of potential intervention strategies, economic costs should also be considered in future modelling work.

It is known that *T. gondii* is not homogeneously distributed in the environment as oocyst deposition by cats depends on cat density and incidence of *T. gondii* infection (Gotteland et al., 2014a). Oocysts are usually concentrated in defecation sites of cats and the contamination level of the environment is associated with season and climatic factors (Schares et al., 2016). The viability of oocysts depends on environmental factors such as humidity, exposure to sunlight and freezing (Dubey et al., 1970; Frenkel and Dubey, 1973). Nonetheless, we could only identify one study describing a model to study the spatial pattern of environmental contamination by *T. gondii*. This type of modelling is mainly hampered by the complexity of integrating the behavior of intermediate and definitive hosts, contamination and infectivity of *T. gondii* oocysts in the environment, and the characteristics of the landscape (Gotteland et al., 2014b). Parameters like detection and survival of oocysts in environmental samples, transmission rate from the environment to cats and rodents, and daily behavior of the hosts are often difficult or unfeasible to quantify. For example, the probability of rodent infection following ingestion of one oocyst was set to one in the model by Gotteland et al.

(2014b). However, in reality the viability of oocysts in the environment may be influenced by the duration and conditions of oocyst exposure in the environment. Therefore, more spatial modelling studies to estimate the risk of contamination by *T. gondii* oocysts would help to get more accurate results when the data gaps are filled.

Only one of the included studies described a model for an outbreak investigation (Shonkwiler and Thompson, 1982). The authors used a discrete-time stochastic model to study an outbreak of toxoplasmosis which occurred among those who visited a riding stable in Atlanta, Georgia, in 1977, and investigated the role of location and frequency of visits in epidemic curve. A few outbreaks of acute toxoplasmosis in humans linked to oocysts have been reported worldwide (Bowie et al., 1997; Coutinho et al., 1982; Ekman et al., 2012). However, outbreak investigations are usually hampered by the lack of detailed information.

In conclusion, considering the high disease burden caused by this parasite, few mathematical models for studying the transmission dynamics of *T. gondii* have been published to date. This systematic review provides an overview of the existing mathematical models and summarises the results according to the purposes of the selected studies. The models vary in their structures, assumptions, measured outcomes and investigated intervention strategies. It is clear that a limitation for several of the current mathematical models is the failure to include all relevant transmission routes present in the life cycle of *T. gondii*. Moreover, due to the absence of field data, assumptions often have to be made, which leads to uncertainty of the predicted values and make the models difficult to validate and compare. Therefore, currently it is difficult to draw specific conclusions on the most effective prevention and control strategies to reduce the burden of toxoplasmosis. Future field work and experiments should include data collection in line with data requirements for these models. In this way, the identified models can be updated and extended to aid the development of effective toxoplasmosis prevention strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This article is based upon work in collaboration with the COST Action FA 1408, the European Network for Foodborne Parasites (Euro-FBP), supported by Cost (European Cooperation in Science and Technology; www.cost.eu).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fawpar.2020.e00102.

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