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Trends in
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Opinion

Is the incidence of congenital toxoplasmosis declining?

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Prenatal infection with the protozoan parasite *Toxoplasma gondii* can cause congenital toxoplasmosis (CT), an often fatal or lifelong-disabling condition. Several studies of human populations have reported temporal decreases in seroprevalence, suggesting declining CT incidence. However, the consistency of this trend among diverse populations remains unclear, as does its implication for prenatal screening programmes, the major intervention against CT. Using temporally resolved data on the seroprevalence of *T. gondii* in various countries, we discuss how the parasite's changing epidemiology may affect trends in CT incidence in varying and counterintuitive ways. We argue that parasite stage-specific serology could be helpful for understanding underlying causes of secular changes in seroprevalence. Furthermore, we highlight the importance of updating cost-effectiveness estimates of screening programmes, accounting for neuropsychiatric sequelae.

Highlights

An emerging body of evidence indicates that exposure to *Toxoplasma gondii* is decreasing among numerous human populations, though most data are from high-income countries.

Considering this changing epidemiology, the cost-effectiveness of prenatal screening programmes should be re-examined while accounting for other (not currently considered) sequelae of congenital toxoplasmosis (CT), including possible neuropsychiatric effects.

Parasite stage-specific serology should be further developed and applied to serum samples from animals and humans to understand the possible causative mechanisms underlying seroprevalence decreases.

The effect of seroprevalence declines on the incidence of CT will be context specific, varying according to parasite genotype, population demographics, and the local epidemiology.

T. gondii: a cosmopolitan parasite

Globally, serology indicates that approximately one in three people have been exposed to *T. gondii* [1], a coccidian parasite with a complex life cycle involving multiple hosts and modes of transmission. All members of the family Felidae are the **definitive hosts** (see Glossary), excreting sexual stage **oocysts** that infect **intermediate hosts** and **secondary hosts**, including mammals (terrestrial and marine [2]) and birds. Infected hosts harbour, potentially for life (but see [3]), asexual stage **bradyzoites** within tissue cysts in skeletal muscle and various, predominantly immune-privileged, organs. Ergo, eating undercooked or raw meat from infected hosts represents a significant source of exposure. Once ingested, oocysts and bradyzoites differentiate into asexual **tachyzoites** that disseminate infection throughout the host. While likely uncommon, *de novo* postnatally acquired infection with tachyzoites can occur through, for example, drinking contaminated unpasteurised milk, receiving an infected blood transfusion [4], using contaminated needles [5], or sexual transmission by contaminated seminal fluid (controversial in humans, but undisputed in other mammals such as sheep, goats, and dogs) [6]. Tachyzoites are responsible for vertical transmission in *T. gondii*-naïve pregnant women infected via any parasite stage. The probability of transplacental passage of tachyzoites is positively related to the gestational age of infection, whereas the severity of sequelae is inversely related. Hence, while first-trimester infections are less likely to lead to vertical transmission, they lead to the most severe disease and are associated with the highest risk of foetal loss [7].

In immunocompetent humans, only 10–20% of postnatally acquired infections have been reported to result in apparent morbidities (usually nonspecific febrile symptoms) [7]. **CT** accounts for almost two-thirds of the estimated 1.9 million disability adjusted life years (DALYs) [8] associated with *T. gondii*, with an estimated 190 000 cases annually (as of a 2013 global meta-analysis; for a more recent review, see [9]) [10]. CT is associated with foetal loss and neonatal death in ~3% of cases [10] and a range of craniocerebral and ocular sequelae, including the 'classical triad' of **chorioretinitis** (often bilateral), **hydrocephalus**, and **intracranial calcifications** [7,11]. While

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approximately 75% of cases are subclinical at birth, symptoms may onset many years or even decades later [7].

Robust data on the incidence of CT are generally limited to the few countries with prenatal screening programmes (i.e., nationwide, routine screening is conducted only in Austria, France, and Slovenia [12]) and hence incidence is likely substantially underestimated worldwide. Even in countries with nationwide screening, publicly available estimates of CT incidence are, with few exceptions [13], not temporally stratified (e.g., incidence from Austria's screening programme is reported as a mean between 1992 and 2008 [14]). This makes it challenging to evaluate temporal trends from publicly available information, despite reports of decreases in seroprevalence over recent decades [15]. Alternatively, more widely available IgG seroprevalence data in pregnant women [1,16] (indicative of cumulative lifetime exposure) can be used to infer CT incidence using statistical and mathematical modelling [13,17–19].

Here, we compile published longitudinal IgG seroprevalence data to show clear evidence of secular declines in human exposure to *T. gondii* across multiple countries. Using epidemiological theory and illustrative modelling, we infer the effect of declining exposure on temporal trends in CT incidence in different epidemiological and demographic contexts. We discuss the implications of changing CT incidence on the cost-effectiveness of interventions against toxoplasmosis, including screening programmes, in different epidemiological and income contexts and conclude by suggesting avenues for future research.

Temporally declining seroprevalence: data-driven or dogma?

Various reports over the past five decades have indicated declines in the seroprevalence of *T. gondii* at varying scales, ranging from communities and subpopulations (e.g., close-knit religious groups in the US [20]; HIV-infected US military personnel [21]), to subnational regions and cities (e.g., South Yorkshire, UK [22]; Stockholm, Sweden [17]) and whole countries (e.g., as reported in the French National Perinatal Survey [23], or the US National Health and Nutrition Examination Survey [24,25]). But whether these declines are consistent among disparate subpopulations, regions, and countries has not been explored.

We therefore conducted a PubMed search of the published literature until 15 April 2022 (employing a 'snowballing' approach [26] to identify additional relevant articles) to identify and extract longitudinal seroprevalence data from populations with two or more comparable datapoints (e.g., collected from individuals from the same country, region, and population or subpopulation). We identified 39 studies conducted in 19 countries from four continents between 1962 and 2018, reporting 121 datapoints on >269 000 individuals (exact sample size not available for some studies) (Figure 1, Key figure). Most of these countries (78.9%, 15/19) are high-income according to the World Bank 2021 classification, with the remainder defined as upper-middle income [27].

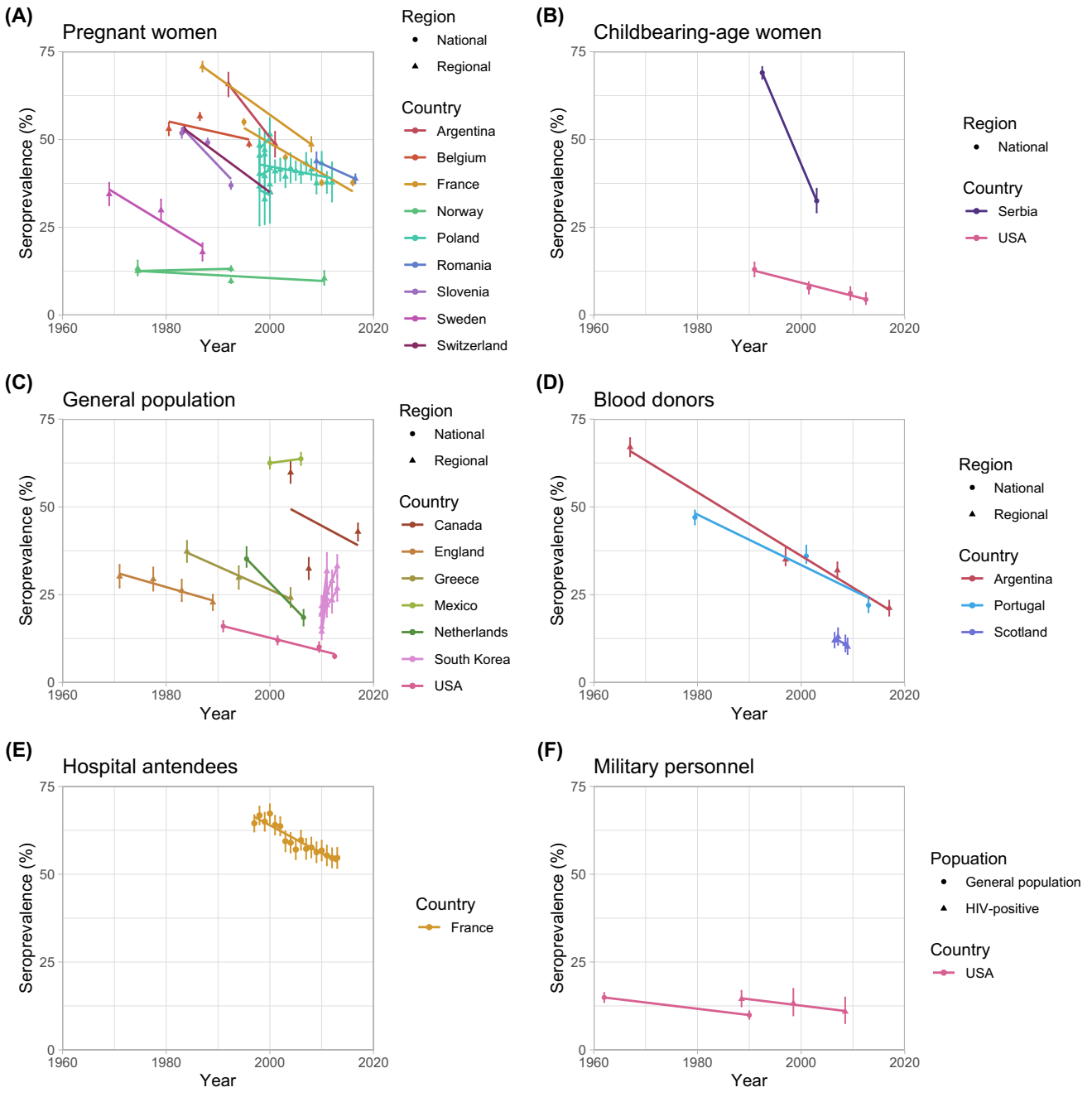
The extracted data were consistent with declines in seroprevalence in most countries, regions, and subpopulations (Figure 1A–F). National survey data (probably the most reliable indication of longitudinal trends) on pregnant women in France and Slovenia, and on childbearing age women in Serbia and the USA, showed stark declines in seroprevalence (Figure 1A,B). (National screening data from Austria also showed declines in seroprevalence from ~50% in the late 1970s to 36.7% in 1989–1991, but the full text and hence the data were inaccessible [28].) National data representative of the general population in The Netherlands and the USA indicated similar declines (Figure 1C) [24,25,29]. Declines were also evident in subpopulations, including blood donors (Figure 1D), hospital attendees (Figure 1E), and military personnel (Figure 1F), and in within-country regional data (Figure 1A–F).

Glossary

Bradyzoite: an asexual, slowly dividing, sessile parasite stage that forms tissue cysts in skeletal muscle and various organs.
Chorioretinitis: scarring of the choroid layer of the retina resulting from prenatal or postnatal infection, leading to reductions in visual acuity or even blindness.
Congenital toxoplasmosis (CT): disease resulting from prenatal infection and subsequent vertical transmission from mother to foetus; includes a wide range of sequelae, which can be fatal (abortion, stillbirth, foetal loss), or otherwise chronically disabling (chorioretinitis, intracranial calcifications, and hydrocephalus, among others).
Definitive hosts: the only species in which the sexual stage of the parasite (oocysts) can develop in the small intestine: felids (domestic and wild cats).
Hydrocephalus: an accumulation of cerebrospinal fluid in the brain; a sequela of CT.
Intermediate hosts: prey species of the definitive hosts, which will vary by geography and definitive host.
Intracranial calcifications: calcifications in the brain, which may be singular or multiple; a sequela of CT.
Mother–child transmission ratio (MCTR): the probability that a prenatal infection leads to infection of the foetus (this probability increases with increasing gestational age, as the placenta becomes increasingly permeable).
Oocysts: the sexual, environmentally resistant, stage of the parasite excreted in the faeces of infected definitive hosts; each sporulated oocyst contains four infectious sporozoites.
Secondary hosts: non-prey species of the definitive hosts, which will vary by geography and definitive host.
Sheep vaccination: the only commercially available *T. gondii* vaccine, based on live attenuated S48 strain 'incomplete' tachyzoites that are unable to form tissue cysts, is licensed for use in sheep. Vaccination is used to reduce the risk of abortion in breeding ewes, with a 2 ml intramuscular injection of $\geq 10^5$ live tachyzoites administered at least 3 weeks before tupping.
Tachyzoites: an asexual, rapidly multiplying stage that disseminates infection throughout the host. Transplacental passage of tachyzoites is responsible for prenatal infection and CT.

Key figure

Trends in immunoglobulin G (IgG) seroprevalence among human populations



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Exceptions to the trend of declining seroprevalence included pregnant women in Oslo and northwest Norway (Figure 1A) [30–32], pregnant women in rural areas and towns of Poznań, Poland (Figure 1A) [33], the national population of Mexico (Figure 1C) [34], and regional populations of islandic and mainland South Korea (Figure 1C) [35–37]. Apparent increases in seroprevalence were also noted in Cali, Colombia [38] and in Malaysia [15], but the full texts of older studies were inaccessible. Excepting Norway, studies indicating temporal stability or increases in seroprevalence tended to have been conducted over shorter time periods (e.g., 1998–2000 for Poznań, Poland, 2000–2006 for Mexico, and 2010–2013 for South Korea) and hence it is difficult to determine longer-term trends.

What is driving changing seroprevalence?

The decline in seroprevalence likely has various nonmutually exclusive explanations that relate to reductions in human exposure to one or more parasite stages (Figure 2). Intensive farming practices that lower the risk of livestock infections (albeit often with reduced animal welfare standards) are thought to decrease human exposure to *T. gondii* bradyzoites [39] (Figure 2). Evidence supporting this notion predominantly comes from seroprevalence surveys of livestock destined for human consumption. For example, in the USA, seroprevalence in grower/finisher pigs (sampled from sites which represented >90% of the country's pork production) declined from 3.2% in 1995 to 2.6% in 2006 and 0.8% in 2012 [40]. Even starker seroprevalence decreases were observed amongst slaughtered intensively farmed pigs in Austria [41]. Although viable tissue cysts may not be present in meat from every seropositive animal (since they are sporadically distributed across tissues and hosts; see [42] for a comprehensive review), these data suggest that reduced parasite exposure in livestock could partly explain seroprevalence declines in people. Other bradyzoite-centric explanations include improvements in biosafety measures, like sufficiently cooking (or freezing) meat prior to consumption [43], and **sheep vaccination** (although this is used only in France, Ireland, New Zealand, and the UK [44]) [45,46] (Figure 2).

Oocyst-centric explanations for declining seroprevalence include improvements in water, sanitation, and hygiene (WASH, e.g., the availability of uncontaminated drinking water, and washing of fruit and vegetables), covering of play sand pits, sterilisation or culling of stray cat populations, keeping cats indoors, and feeding cats dried or commercial pet food instead of raw meat [47,48] (Figure 2).

Tachyzoite-centric explanations could include improvements in pathogen screening of prospective blood donors, safe needle use and milk pasteurisation, although reductions in *de novo* tachyzoite infections are unlikely to explain a significant portion of the overall trend of decreasing seroprevalence (Figure 2).

Some interventions, like screening and health education, are likely to decrease exposure to all parasite stages (Figure 2).

Figure 1. IgG seroprevalence in different populations according to median sampling year (39 studies reporting 121 datapoints for >269 000 individuals from 19 countries representing four continents). The observed data and 95% confidence intervals (CIs) are represented by points and error bars, respectively. Lines show the linear estimated change in seroprevalence, with year as the predictor and seroprevalence as the response variable, for a given country (or, in cases of two or more populations per country, a given population). Data were collected from PubMed on 15 April 2022, using search terms *(national OR representative) AND (seroprevalence OR serosurvey) AND (toxoplasma gondii OR toxoplasma OR toxoplasmosis) AND (longitudinal OR decreased OR decreasing OR increased OR increasing OR temporal)*. A 'snowballing' approach was used to identify additional relevant data cited within the articles [26]. Data were included if there were two or more datapoints per population (grouped in the following order: country, region, population, subpopulation). If missing, the number of positive individuals was calculated by multiplying the seroprevalence (as a proportion) by the total number of individuals. Binomial 95% CIs were calculated using the Pearson–Klopper exact method. The code and data used to produce this plot are available online: https://github.com/gcmilne/temptrends.

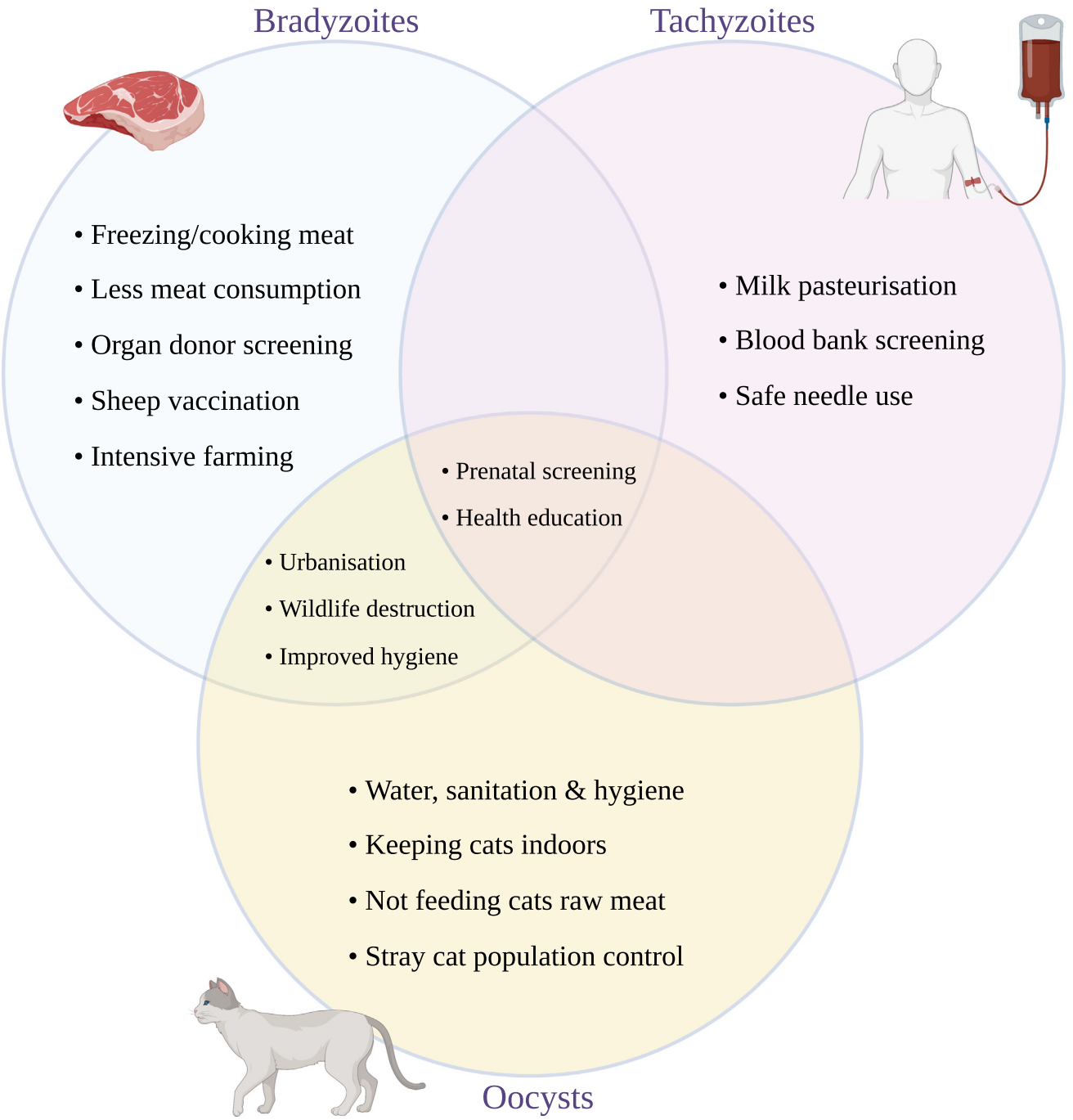

Figure 2. Possible drivers of changing parasite exposure. How interventions or cultural changes may be reducing human exposure to one or more *Toxoplasma gondii* parasite stages and hence may be responsible for a declining seroprevalence. Figure created with BioRender (www.BioRender.com).

Implications for the incidence of congenital toxoplasmosis

Declines in seroprevalence are often associated with high-income countries only [49]; yet the dearth of longitudinal data from lower-middle-income countries (LMICs) must be acknowledged. For

example, recent global systematic reviews of *T. gondii* seroprevalence in pregnant women found that only 3.1% (14 320/464 162) [1] and 1.8% (15 937/902 228) [50] of the data were from LMICs. Hence, although it can be argued that many possible factors contributing to decreasing seroprevalence are less applicable to LMICs, the lack of data preclude solid inference on this.

Declining exposure to *T. gondii* (indicated by a declining seroprevalence) will most often correspond to reductions in the incidence of CT, as the risk of exposure during a susceptible pregnancy diminishes (excepting 'peak shift' dynamics [51] in highly endemic settings; Box 1). Notwithstanding, the degree of correlation between declining exposure and CT incidence will be context-specific, varying according to epidemiological factors like the **mother–child transmission ratio (MCTR)** and the proportion of cases leading to clinical disease (which are both also influenced by prenatal treatment [52], parasite genotype [53], and other host factors [54]), and the population demographic structure and fertility rate (which vary by year and country income status [55]).

A major epidemiological factor relevant to CT prognosis is parasite genotype. Population studies have indicated higher genetic diversity of *T. gondii* in the Americas (including a preponderance of 'atypical' strains that belong to haplogroups 4–16 [56]) compared to the largely clonal population structure (type I–III strains corresponding to haplogroups 1–3) in Africa, Asia, and Europe (e.g., 90.5% of cases in France are type II) [53]. This geographic variability has been hypothesised to map to variability in MCTR and virulence [53,57]. For example, a systematic review revealed that type I parasites more frequently infect before the third trimester compared to type II or III parasites [53]. Moreover, neonates congenitally infected with type I or atypical strains have 2.5-times greater odds of clinical sequelae compared to those infected with-type II or III strains [53]. Furthermore, in the USA, infants congenitally infected with mixed, compared to only type II strains had higher probabilities of severe-to-moderate neurological disease [83% (77/93) vs. 63% (33/52)] and severe ocular disease [67% (59/88) vs. 39% (18/46)] [58]. Hence, in countries where type I and atypical

Box 1. Peak shift dynamics: implications for congenital disease incidence

While in many contexts, declining exposure to *T. gondii* will lead to a declining incidence of CT due to fewer seroconversions in pregnancy, this need not always be the case. For example, some authors have noted that despite seroprevalence declines in the initially high-transmission settings of Austria and Poland, CT incidence (or IgM prevalence, indicative of acute infection in pregnancy), conversely, increased [78,79]. These findings are consistent with established epidemiological theory on 'peak shift' dynamics [51]. In settings with a high infection (exposure) rate, most infections are acquired in childhood. If the infection rate reduces, the same cumulative risk of exposure is obtained at a later age and hence the 'peak' of first exposure is shifted into adolescence or adulthood. For congenital diseases obtained through first-time infection in pregnancy, such a dynamic may have critical implications for disease incidence in settings experiencing temporally shifting patterns of exposure. Indeed, a consequence of this dynamic was seen during the 1980s–1990s childhood rubella vaccination programme rollout. In some countries, insufficient vaccine coverage led to a shift in the average age of first infection into peak childbearing ages and a subsequent increase in the incidence of congenital rubella syndrome [80,81].

Similar dynamics could plausibly be predicted to occur in the context of temporally declining exposure to *T. gondii*. To illustrate this, we constructed a simulated cohort to determine the relationship between seroprevalence and CT incidence, with demographic data nominally matched to the UK in 2020 [55]. Using different infection probabilities (to produce varying levels of mean seroprevalence in childbearing ages), this simple example illustrates that, given a sufficiently high-transmission setting, decreases in seroprevalence from a high baseline can lead to increases in CT incidence (Figure IA). This dynamic, which accords with peak shift theory, is due to the inverse relationship between the probability of infection and the average age of first infection (Figure IB) [59]. Intuitively, the highest CT incidences are obtained when the average age of infection coincides with peak childbearing ages (Figure IA–C). Hence, this suggests that highly endemic settings with a declining probability of infection may experience transient increases in CT incidence. In this simple example of a UK-like demographic, the 'threshold' mean seroprevalence in childbearing ages needed to produce this effect is >70%; however, in lower-income countries this threshold seroprevalence would be expected to be lower given that peak childbearing ages tend to be younger [55]. Other complications not accounted for here such as varied rates of infection over age – rather than the age-constant rate implicit in this example (some data indicate a higher rate of exposure among children and young adults which then diminishes into older age groups [81]) – and migration, would also likely change this threshold value.

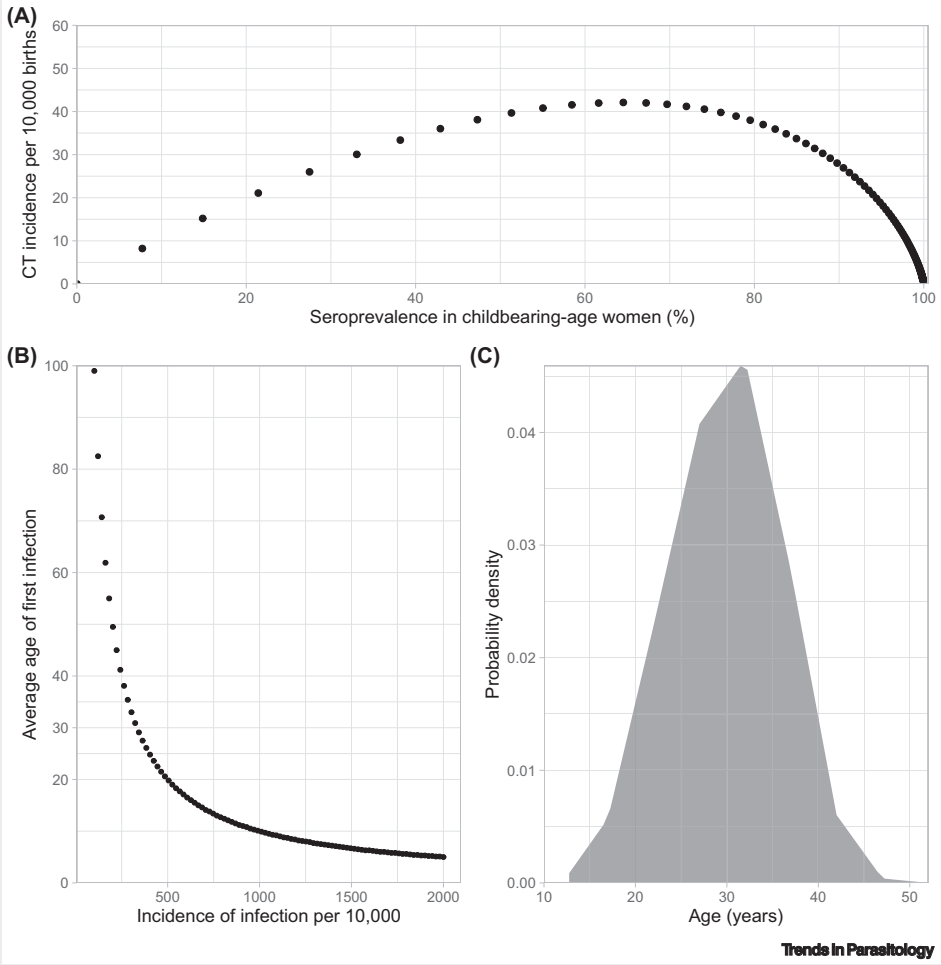

Figure I. The relationship between seroprevalence and congenital toxoplasmosis (CT) incidence. (A) A simulated population was constructed to determine the relationship between seroprevalence in childbearing-age women (calculated as a demographically weighted mean over childbearing ages; with fertility rates matched to the UK in 2020 [55]) and the incidence of CT per 10 000 live births. To estimate the number of new infections per 9-month age interval, in each age group the per capita infection probability (100 values ranging from 0 to 2000 per 10 000 live births per year) was multiplied by the age-specific number of susceptible individuals (derived by the age-specific population size multiplied by the proportion without prior parasite exposure). The population was given a 'flat' structure, with 100 individuals in each age group. The age-specific seroprevalence was then estimated by dividing the cumulative sum of infections until the current age group by the age-specific population size in the index age group. CT cases were defined as the number of first-time infections (seroconversions) in pregnancy (estimated as new infections multiplied by the proportion of the population that is pregnant) multiplied by a mother–child transmission ratio of 44% [63]. CT incidence was estimated by dividing the total CT cases by the number of births (estimated by multiplying the age-specific population size by the proportion that are pregnant) multiplied by 10 000, to give an incidence per 10 000 live births. (B) An illustration of how the average age of first infection decreases with increasing annual incidence of infection, with the former being the reciprocal of the latter (as a proportion such that, for example, an incidence of 500 per 10 000 would become 0.05) [59]. (C) Empirical probability density of age-specific fertility rate among women in the UK population in 2020 (data from the United Nations [55]). The code used to produce this plot is available online: https://github.com/gcmilne/temptrends.

strains dominate, like those in Central and South America, seroprevalence decreases might lead to a lesser reduction in symptomatic CT incidence compared to comparable reductions in seroprevalence in type II-dominant countries, such as those in Europe.

Recent studies have also demonstrated a significant positive link between parasite burden in amniotic fluid and the severity of clinical symptoms in congenitally infected neonates (reviewed in [53]). Since particular genes found within type I parasites are associated with increased parasite growth (e.g., those encoding ROP16 and ROP18) [53], this may provide a mechanistic explanation for the association between parasite genotype and host clinical symptoms, though this is at present highly speculative.

Demographics also play a key role in influencing the incidence of CT in different settings. Since CT most commonly occurs following first-time exposure in pregnancy, incidence depends on both the proportion of women susceptible at a given age and the age-fertility distribution. In high-income countries, pregnancies generally peak at older ages compared to LMICs [55]. Average age of infection is inversely related to the rate of exposure [59], and therefore a relatively lower rate of exposure would cause a higher CT incidence in high-income countries compared to LMICs (i.e., in high-income countries, the overlap between peak childbearing ages and the peak age of first infection occurs at a lower exposure rate). Temporal changes in demographics (e.g., increases in mean childbearing ages) may further interact with changes in exposure to elicit complex changes in CT incidence, including so-called 'peak shifts' (Box 1) [51].

Implications for interventions against congenital toxoplasmosis

The decision to implement prenatal or neonatal screening programmes is primarily based on cost-effectiveness analysis. For prenatal screening, cost-effectiveness is heavily influenced by seroprevalence in pregnant women which determines the number of susceptible individuals requiring follow-up serological testing. For example, considering together *T. gondii*-specific sequelae and those from other foetal infections, the cost per outcome avoided by prenatal screening is an estimated 56% higher in a USA-like country (with a seroprevalence of 10%) compared to in France (with a seroprevalence of 37%), at €23 168 versus €14 826 [60]. Hence, prenatal screening programmes may become increasingly expensive (and less cost-effective) in countries where exposure (and seroprevalence) is decreasing. This has been highlighted by a French study estimating that decreasing seroprevalence necessitates the use of an additional 93 000 tests every year, resulting in an annual incremental increase in the cost of screening of €1 million [61].

Neonatal screening is less costly than its prenatal counterpart, but it is generally considered to be less cost-effective since it does not reduce the risk of foetal infections resulting in prenatal injuries or losses [60]. This strategy relies on systematic screening of neonates for the presence of *T. gondii*-specific IgM and/or IgA antibodies as indicative of acute infection with the aim of reducing the severity of CT through postnatal treatment (unlike prenatal screening which focuses on prenatal treatment to lower the MCTR and risk and severity of sequelae).

Several key and uncertain factors influence the estimated cost-effectiveness of both prenatal and neonatal screening strategies. These include: the performance of diagnostics in identifying CT (IgM serology on pregnant women has poor sensitivity for detecting acute infections, leading to many false negatives [62]), and the efficacy of treatment for reducing the MCTR (prenatal screening) and the severity of CT (prenatal and neonatal screening). Treatment efficacy is particularly controversial, largely because of a lack of randomised controlled trials, although observational data have shown that prenatal treatment reduces two- to sixfold the odds of materno-foetal transmission [14,63]. The efficacy of prenatal and early neonatal treatment on clinical sequelae is even more uncertain, with different observational studies reporting heterogenous results [11].

The local geographic preponderance of type I and atypical genotypes (leading to an increased risk of severe outcomes among CT cases) may be another important factor influencing the

cost-effectiveness of screening. Since a larger proportion of first-time maternal infections in type I/atypical-dominant, compared to type-II-dominant, regions may result in symptomatic CT, prenatal screening programmes might also be expected to be more cost-effective in the former regions (assuming similarities in treatment efficacy across parasite genotypes [64]).

While increases in the cost per case averted of prenatal and neonatal screening programmes are inevitable with declining exposure in already low- to moderate-endemic settings, the cost-effectiveness of both approaches crucially depends on the sequelae perceived to result from *T. gondii* infection. Currently, other health conditions associated with *T. gondii* exposure – such as later-onset neuropsychiatric sequelae, ischemic heart disease, and certain cancers (the burdens of which may be substantial) [65,66] – are not considered. Other rarely considered (indirect) benefits of screening might include early recognition of pregnancy issues (*T. gondii*-related or otherwise) through regular doctor's visits; and health education-driven improvements in risk-mitigating behaviours towards other foodborne pathogens [60]. Not accounting for these factors may thus engender significant underestimation of screening cost-effectiveness. Finally, cost-effectiveness calculations do not account for possible 'peak shift' dynamics [51] in highly endemic settings. Peak shifts would transiently increase the incidence of CT and hence also the cost-effectiveness of screening (Box 1). Together, these factors suggest that current cost-effectiveness calculations are likely yielding substantial underestimates.

Future directions

Representative seroprevalence and CT data from a greater variety of countries – particularly of lower income – are needed to understand more completely the changing epidemiology of *T. gondii* in humans. Serological, risk factor, and parasite strain data among domesticated and sylvatic host populations are also essential for a holistic understanding of the interacting ecology and epidemiology. Deidentified data from national screening programmes should be made publicly available and be adequately temporally resolved to permit robust epidemiological monitoring. The availability of more trimester-specific and strain-level data will also be invaluable for identifying possible causative mechanisms explaining decreasing parasite exposure.

Parasite stage-specific serology [67] applied to serum samples from animals and humans could be used to better understand drivers of declining/changing exposure and help to disentangle the relative contributions to transmission of environmental oocysts versus foodborne bradyzoites [68,69]. This approach has already been used to uncover the (previously underappreciated) epidemiological importance of oocyst infections in Brazil [69–71] and the USA [72]. Moreover, stage-specific serology could be used to determine whether MCTRs differ between routes of exposure, building on laboratory studies that found a higher likelihood of congenital infection following oocyst exposure in gravid rats (reviewed in [73]). Wider availability and standardisation of stage-specific assays [68] will have a transformative effect on our understanding of *T. gondii* epidemiology and disease.

Improvements in CT diagnostics and treatment will be vital for improving the cost-effectiveness of screening programmes, particularly with a declining incidence of disease. The recent development of rapid, inexpensive, and highly sensitive and specific point-of-care tests [74] could make screening more affordable in resource-poor countries – and their widespread adoption could begin to address the dearth of data in these settings. Unlike conventional serology, point-of-care tests do not require skilled technicians, nor expensive equipment [74]. While most CT is treated with spiramycin and pyrimethamine-sulfonamide combinations, the development of more efficacious drugs – including for individuals with glucose-6-phosphate dehydrogenase deficiencies (ordinarily a contraindication for treatment) [75] – will be necessary to improve and sustain cost-effectiveness.

Finally, it is paramount that epidemiological studies are initiated to assess the long-term burden of neuropsychiatric sequelae associated with *T. gondii* [66,76]. The inclusion of strain typing (while recognising the trimester of infection) will be valuable to corroborate the association between type I congenital infection and an increased risk of affective disorders in adulthood [77]. Such studies should be particularly feasible in countries with routine prenatal or neonatal screening programmes and ideally should be designed to infer causality by identifying the temporality of the *T. gondii*-disease association (e.g., cohort studies). Data generated from these studies could inform updated calculations of the cost-effectiveness of screening (since neuropsychiatric sequelae are missing in current evaluations [60]) and estimates of the global burden of toxoplasmosis.

Concluding remarks

An emerging body of evidence suggests that human exposure to *T. gondii* is declining in many high-income countries, yet the specific drivers of this trend remain elusive (see Outstanding questions). New epidemiological surveys and greater availability of existing epidemiological data could corroborate this trend, particularly in lower income settings. The underlying drivers of these trends could be better understood using techniques to interrogate the source of animal and human infections, including through the further development and application of parasite stage-specific serology. In parallel, novel epidemiological studies should investigate the 'invisible' burden of toxoplasmosis, particularly *T. gondii*-associated neuropsychiatric sequelae. Ultimately, this will improve understanding of *T. gondii* epidemiology and inform the future design of mitigating strategies against this disabling parasitic infection.

Outstanding questions

What are the epidemiological drivers of seroprevalence declines in people?

Are the seroprevalence declines seen among high income countries also observed across countries of lower income statuses?

What proportion of treated and untreated cases of CT develop neuropsychiatric sequelae?

How do factors such as parasite genotype and the trimester of infection affect the likelihood of later life neuropsychiatric sequelae in congenitally infected infants?

Are neuropsychiatric sequelae more likely when infection occurs prenatally (compared to postnatally)?

How often do other forms of *T. gondii* vertical transmission occur (e.g., superinfection with a distinct parasite strain, or reactivation of a pre-existing latent infection)?

Does the infecting parasite stage (e.g., oocyst or bradyzoite) alter the risk of vertical transmission?

Does coinfection with another pathogen influence the probability of *T. gondii* vertical transmission and of the sequelae of CT?

Does accounting for the indirect benefits of prenatal screening, alongside possible neuropsychiatric sequelae of CT, offset the reduced cost-effectiveness of such programmes in the context of declining exposure?

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Declaration of interests

The authors declare no competing interests.

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