BMJ Open Global, regional and national estimates of *Toxoplasma gondii* seroprevalence in pregnant women: a protocol for a systematic review and modelling analysis

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ABSTRACT

Introduction To set priorities for public health policy, funding for public health interventions, and healthcare planning which will ultimately contribute in bending the burden of toxoplasmosis towards maternal and neonatal health, it is necessary to have accurate data on the prevalence of toxoplasmosis in pregnancy. Therefore, we aimed to estimate the seroprevalence of *Toxoplasma gondii* infection in pregnant women by countries, WHO regions and globally.

Methods and analysis We will search multiple databases to identify studies that reported the prevalence (or enough data to compute this estimate) of *Toxoplasma gondii* in the global population of pregnant women up till December 31, 2018 without any language restrictions. Study selection, data extraction and risk of bias assessment will be conducted independently by three pairs of investigators. For each country, we will estimate the prevalence based on empirical studies if there is either one nationally representative study, or two or more not nationally representative studies. Then, we will perform a country-specific random-effects meta-analyses. The heterogeneity will be evaluated using the χ^2 test on Cochrane's Q statistic and quantified with H and I² statistics. For countries with one or no empirical studies or where the meta-analysis will result in a wide CI of 0%–100%, we will predict the country's prevalence by using a Bayesian generalised non-linear multilevel model. The model will have a hierarchical structure in which estimates for each country will be informed by its own data, if available, or by data from other countries in the same WHO region.

Ethics and dissemination Since this study will be based on published data, it does not require any ethical approval. Its findings will be published in a scientific peer-reviewed journal. They will also be presented at scientific conferences and to relevant public health sectors.

PROSPERO registration number CRD42019125572.

INTRODUCTION

Toxoplasmosis is a zoonotic food-borne infection caused by the parasite *Toxoplasma gondii* with a wide range of clinical syndromes in humans.¹ This obligate intracellular protozoan parasite is found in 30% of the

Strengths and limitations of this study

- To the best of our knowledge, this work will be the first systematic review, meta-analysis and modelling analysis reporting the prevalence of toxoplasmosis in pregnant women at global, regional and country levels.
- This study will inform and guide policy and practice in decision-making and guide researchers in future investigations in the field of toxoplasmosis in pregnancy.
- Independent reviewers will perform the study selection, extract data and assess the methodological quality included studies.
- The study could be limited by scarcity of data for some countries.

global population with substantive differences between countries.² Humans can be infected through ingestion or handling of undercooked or raw meat containing toxoplasma cysts. Human infection can also occur during direct contact with felines or from the consumption of water or food contaminated with faeces containing oocysts from infected felines, especially cats.²

For women, infection with *T. gondii* during or just before pregnancy can be particularly serious resulting in miscarriage, stillbirth, foetal death, neurologic and neurocognitive deficits, chorio-retinitis or child disability.^{3 4} Globally, it is estimated an average of 190 100 incident cases of congenital toxoplasmosis yearly, with 1.5 neonatal cases occurring per 1000 live births.⁵ This infection among pregnant women requires early diagnosis and treatment to improve mother and child health.⁶

To set priorities for public health policy, funding for public health interventions and healthcare planning for curbing the burden

of toxoplasmosis on pregnancy outcomes and neonatal health, it is necessary to have accurate data on the prevalence of toxoplasmosis in pregnancy. However, to date, most countries do not have prevalence data at a population-based level among pregnant women. Furthermore, and to the very best of our knowledge, these prevalence rates have not yet been estimated at global, regional and country levels. To fill these knowledge gaps, we aimed to estimate the seroprevalence of *T. gondii* infection in pregnant women, by countries, WHO regions and globally. This study will provide the best understanding of the scope of this public health concern and is intended to inform and draw the attention of researchers, healthcare practitioners, public health authorities, policy makers and governments towards the pending burden of toxoplasmosis in pregnancy.

METHODS AND ANALYSIS

Design and registration

This systematic review and meta-analysis protocol will be conducted following the Centre for Reviews and Dissemination guidelines.⁷ This protocol was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).⁸ The study protocol was registered with PROSPERO, CRD42019125572.

Criteria to consider studies for this review

1. Types of studies: We will consider cross-sectional studies, baseline data of cohort studies, baseline data of non-intervention arms of clinical trials and surveillance data. We will exclude case reports, letters, comments, editorials, reviews and case series (<30 participants).
2. Types of participants: We will consider studies conducted in pregnant women. Studies conducted in pregnant women selected based on the presence of a specific disease or a condition like HIV infection will be excluded.
3. Types of outcomes: We will consider studies reporting the seroprevalence of *T. gondii* infection based on the presence of immunoglobulins G and/or immunoglobulins M in the serum (or enough data to compute this estimate that is, cases of toxoplasmosis infection and sample size of pregnant women).

Search strategy for identifying relevant studies

The following databases will be considered: Medline through PubMed, Excerpta Medica Database (EMBASE), Web of Knowledge, Current Contents Connect, KCI-Korean Journal Database, Russian Science Citation Index, Scientific Electronic Library Online (SciELO) Citation index, Africa Journal Online (AJOL), Literatura Latino Americana em Ciências da Saúde (LILACS), Index Medicus for South-East Asia Region (IMSEAR), Western Pacific Region Medicus (WPRIM), Index Medicus for the Eastern Mediterranean Region (IMERMR), Africa Index Medicus (AIM), and Global Index Medicus up to December 31, 2018. We will search records regardless of

language of publication and geographic situation. The search strategy in all databases is presented in the online supplementary table 1. The reference list of eligible articles and relevant reviews will be manually searched to identify additional studies. Key search terms will include: “pregnant women”, “pregnancy”, “toxoplasmosis” and “toxoplasma”.

Selection of studies for inclusion in the review

Two investigators (JJB and JRN) will use the Rayyan application⁹ to independently select records based on the titles and abstracts. Any disagreement will be solved by discussion and consensus. Studies in language different of English or French will be translated using Google Translate and considered for eligibility. These investigators will independently evaluate the full text of selected records. Agreements between the two investigators will be estimated by the Cohen's kappa coefficient.¹⁰

Methodological quality assessment

Assessment of the methodological quality of finally included studies will be performed with the Joanna Briggs Institute tool for prevalence studies (online supplementary table 2).¹¹ This is a nine-item tool. The defined questions will be scored with 0 for “No” or “Unclear” and 1 for “Yes”. The total score of each article will be calculated by the sum of its points. Based on this tool, studies will be rated as low risk, moderate risk and high risk of bias with corresponding scores between 0–3, 4–6 and 7–9, respectively. Discrepancy in risk of bias assessment among the three pairs of investigators (JNT, DNT, AOB, NSY, PSS, and JJB) will be solved by discussion and consensus or arbitration by another investigator (JRN).

Data extraction and management

Data extraction will be done independently by three pairs of investigators (JNT, DNT, AOB, NSY, PSS and JJB). Disagreements in each pair of investigators will be solved by discussion or will involve another review author for arbitration (JRN), if necessary. Using a pretested form, we will extract:

1. Bibliometric information: last name of the first author and year of publication.
2. Characteristics of the study: country, period of inclusion of participants, timing for blood collection for laboratory analysis (during pregnancy and/or delivery), site (antenatal care unit, delivery unit, hospital-based, and population-based) and representativeness of the sample (national, regional/multisite, one site). The countries will be grouped in regions according to the WHO regional classification: Africa, Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific.
3. Prevalence data: number of pregnant women tested for *T. gondii*, how they sampled (probabilistic sampling vs non-probabilistic sampling) and number of pregnant women infected with the protozoa. Where cases and samples for estimating the prevalence will not be

available, we will contact the study's corresponding author to request the missing information.

Data synthesis and analysis

Analyses will be performed with the statistical software R (The R Foundation for statistical computing, V.3.6.1, Vienna, Austria). For each country, we will estimate the prevalence based on empirical studies if there are (1) one nationally representative study or (2) two or more non-nationally representative studies. Then, we will perform country-specific random-effects meta-analyses.¹² We will use generalised linear models to pool prevalence estimates.¹³ Heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic,¹⁴ which will be quantified by I^2 values. The I^2 statistic estimates the percentage of total variation across studies due to true between-study differences rather than chance. In general, I^2 values greater than 60%–70% indicate the presence of substantial heterogeneity.¹⁵ Publication and selection bias will be assessed visually by inspection of funnel plots that will be generated. The formal Egger's test will serve for detecting the presence of publication bias.¹⁶ A p-value < 0.10 on Egger's test will be considered indicative of statistically significant publication bias. A priori, it was decided that if publication bias is present, it would not be adjusted for, since we believe that the prevalence estimates of interest would likely be published even if substantially different from previously reported estimates. Unadjusted prevalence will be recalculated based on information of crude numerators and denominators provided by individual studies. Prevalence will be reported with their 95% confidence and prediction intervals.

For countries with one or no empirical studies or where the meta-analysis will result in a CI of 0%–100%, we will predict the country's prevalence by using a Bayesian generalised non-linear multilevel model with a binomial family and a logit link to restrict predictions to values between 0 and 1. We will consider uninformative (objective) priors. The model will have a hierarchical structure in which estimates for each country are informed by its own data, if available, and by data from other countries in the same WHO region. The hierarchical structure shares information to a greater extent when data are non-existent or weakly informative (eg, are not national or only one non-nationally representative study). Country-specific predictor variables that will be considered include gross domestic product per capita, female human development index, female mean years of schooling, gender inequality index and antenatal coverage.¹⁷ The model will incorporate non-linear patterns for all these predictors using a restricted cubic splines function. The final model will be chosen based on goodness of fit (evaluated using pseudo R-squared) and plausibility of the predictions. Predictions will be calculated based on covariate values from the most recent estimate at the time of the analysis.

Protocol development and potential amendments

There was no funder, sponsor or institution involved in the conception and design of this protocol. We do not

plan to make any changes to this protocol. However, if substantial changes occur during the review, they will be reported in the published results.

Patient and public involvement

Patients and public were not involved in the conception and design of this protocol. This is a protocol for a review of already published studies.

Contributors JJB and JRN conceived the protocol and with JNT, DNT, AOB, NSY and PSS designed the protocol. JJB drafted the manuscript. JNT, DNT, AOB, NSY, PSS and JRN revised successive drafts of the manuscript. Guarantor of the review: JJB. All authors approved the final version of the manuscript.

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