Public Health Impact of Congenital Toxoplasmosis and Cytomegalovirus Infection in Belgium, 2013: A Systematic Review and Data Synthesis

Peer-reviewed author version

Smit, G. Suzanne A.; PADALKO, Elizaveta; Van Acker, Jos; HENS, Niel; Dorny, Pierre; Speybroeck, Niko & Devleesschauwer, Brecht (2017) Public Health Impact of Congenital Toxoplasmosis and Cytomegalovirus Infection in Belgium, 2013: A Systematic Review and Data Synthesis. In: CLINICAL INFECTIOUS DISEASES, 65(4), p. 661-668.

DOI: 10.1093/cid/cix344
Handle: http://hdl.handle.net/1942/24377

The public health impact of congenital toxoplasmosis and cytomegalovirus infection in Belgium, 2013: a systematic review and data synthesis

G Suzanne A SMIT[1,2,3,*], Elizaveta PADALKO[4,5], Jos VAN ACKER[6], Niel HENS[7,8,9], Pierre DORNY[1,2], Niko SPEYBROECK[3], and Brecht DEVLEESSCHAUWER[10]

[1]Department of Virology, Parasitology and Immunology, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

[2]Department of Biomedical Sciences, Institute of Tropical Medicine (ITM), Antwerp, Belgium

[3]Institute of Health and Society (IRSS), Université catholique de Louvain, Brussels, Belgium

[4]Department of Clinical Biology, Microbiology and Immunology, Ghent University Hospital, Belgium

[5]School of Life Sciences, Hasselt University, Diepenbeek, Belgium

[6]Laboratory of Clinical Microbiology, AZ Sint-Lucas, Ghent, Belgium

[7]Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Diepenbeek, Belgium

[8]Centre for Health Economics Research & Modelling Infectious Diseases (CHERMID), Vaccine & Infectious Disease Institute, University of Antwerp, Belgium

[9]Epidemiology and Social Medicine, University of Antwerp, Belgium

[10]Department of Public Health and Surveillance, Scientific Institute of Public Health (WIV-ISP), Brussels, Belgium

---

Keywords

Congenital infections, data gaps, burden of disease, DALY

Congenital toxoplasmosis and CMV burden

Quantification of the disease burden of congenital toxoplasmosis and cytomegalovirus infection in Belgium in terms of Disability-Adjusted Life Years (DALYs) and identification of the major data gaps.

*** Corresponding author**

Suzanne Smit, DVM MVSc MSc

Department of Virology, Parasitology and Immunology, Faculty of Veterinary Medicine,

Ghent University, Salisburylaan 133, 9820 Merelbeke, BELGIUM

Tel.: +32 (0)484513799 | Mobile phone: +31 (0)641202041 | E-mail: suzanne.smit@ugent.be

 # Alternate corresponding author

Brecht Devleesschauwer, PhD DVM MVSc MStat

Scientific Institute of Public Health, Department of Public Health and Surveillance,

Rue Juliette Wytsmanstraat 14, 1050 Brussels, Belgium.

Tel.: +32 2 642 50 35 | E-mail: brecht.devleesschauwer@wiv-isp.be

Abstract

Congenital toxoplasmosis (CT) and cytomegalovirus infection (cCMV) may cause significant morbidity or even fetal or neonatal mortality. We aimed to quantify the disease burden of CT and cCMV in Belgium in terms of Disability-Adjusted Life Years (DALYs) and identify data gaps. The public health impact of CT and cCMV in Belgium in 2013 was 188 (95% uncertainty interval [UI]: 43–419) and 1976 (95% UI: 757–4067) DALYs, respectively. The major data gaps identified were representative Belgian studies; information on important sequelae, intra-uterine mortality and termination of pregnancy; and late onset sequelae. A scenario analysis showed important increases in years of life lost when the burden due to fetal losses was included and decreases in DALYs when comprehensive CT prevention measures were conducted. Addressing the key data gaps identified may allow generating the data needed for breaking the vicious circle of under-recognition.

Introduction

Data indicate that congenital toxoplasmosis (CT) and cytomegalovirus (cCMV) infection are important diseases in Belgium [1,2]. These infections can be asymptomatic but can also lead to lifelong disabilities and even fetal or neonatal death [3]. Toxoplasmosis is a zoonosis caused by the parasite *Toxoplasma gondii.* It is commonly assumed that only primary infections of seronegative mothers may lead to CT [4]. CMV is a herpes virus spreading through infected body fluids such as urine or saliva. In contrast to toxoplasmosis, not only primary infections of seronegative women but also recurrent infections (comprising both reactivation and reinfection) of seropositive mothers may cause congenital infections [1,5]. Unfortunately, there is a continued lack of awareness, especially for CMV, and uncertainty around the benefits of prenatal screening and treatment for both congenital infections [5,6,7].

Knowledge about the public health impact of both aforementioned congenital infections can boost overall awareness and is essential for evidence-based health policy, monitoring trends and prioritizing and evaluating the impact and cost-effectiveness of much needed prevention or intervention strategies. We therefore aimed to assess the public health impact of CT and cCMV in Belgium in terms of Disability-Adjusted Life Years (DALYs), and to identify the key data gaps.

Materials and Methods

Incidence

We conducted a systematic review of recent literature (1995–2015) on the seroprevalence and incidence of toxoplasmosis and CMV infections in women of childbearing age and the incidence of both congenital infections in Belgium. The systematic literature search was

conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines [8] (Supplementary appendix 1). We searched PubMed (in April 2016) for relevant English, French, Dutch or German language articles using the following strategy: "(CMV OR cytomegalovirus OR toxoplasm*) AND (Belgi*)" in the title/abstract field, and we scanned the reference lists of eligible papers. Studies were selected that reported seroprevalence and/or incidence of toxoplasmosis or CMV in women of childbearing age and/or incidence of CT or cCMV infections (only if data were based on systematic screening of newborns) in Belgium; were published within 1995–2015; and based on a sample size ≥30. Duplicate data were removed.

Clinical impact

DALY calculations require a disease model, i.e. a schematic representation of the various health states (including sequelae) that are causally related with the pathogen in question [9]. We used the incidence of long-term health outcomes for CT described by Havelaar et al. [10], Kortbeek et al. [11], and Torgerson & Mastroiacovo [12]. The classic triad of clinical manifestations of CT is chorioretinitis, intracranial calcifications and hydrocephalus. Other health outcomes are abnormalities of the central nervous system and fetal or neonatal death. For the occurrence of cCMV sequelae, a meta-analysis was performed on data obtained from the corresponding systematic review by Dollard et al. [13]. Symptomatic infants can present with typical, potentially fatal, generalized cytomegalic inclusion disease (CID) at birth. Long term sequelae associated with cCMV are both unilateral and bilateral sensorineural hearing loss (SNHL); cognitive deficit (CD, including mental retardation, neurological impairment and developmental delay); motor deficit (MD, including any limitation regarding bodily movement and cerebral palsy); visual impairment; and fetal and neonatal death. However, eligible data on visual impairment and mortality were lacking [13]. Although the majority of

congenitally infected infants have no sequelae, they may develop clinical signs later in life, mostly chorioretinitis and hearing loss with CT and cCMV, respectively [10,14]. Havelaar et al. [10] estimated the mean age of CT related late onset chorioretinitis to be ten years old. A survival analysis was performed to estimate the onset of cCMV related hearing loss. For the latter, studies were selected with an average follow-up of five years in which cCMV infected children received repeated hearing evaluations [15,16]. All other sequelae were assumed to be life-long. The Belgian life expectancy table for 2012 [17] was used to estimate the duration of lifelong sequelae. The standard life expectancy table from the GBD 2010 study was adopted for calculating Years of Life Lost (YLLs) [18]. Fetal loss was not taken into account in the main analysis due to too few eligible data, but explored in a scenario analysis.

Public health impact

Based on the information on incidence and clinical impact, the burden of both congenital infections was estimated in terms of DALYs, which combine disease occurrence and clinical impact in a single number [9]. DALYs are the sum of Years Lived with Disability (YLDs, obtained by multiplying the number of incident cases, the duration and DW of the concerned health state) and YLLs (obtained by multiplying the number of deaths and residual life expectancy at age of death). DWs, expressing the relative reduction of health-related quality of life on a scale from zero (perfect health) to one (worst possible health status), were obtained from the Global Burden of Disease (GBD) studies [19]. DWs for CT were updated to GBD 2013 estimates, and, for the first time, DWs were allocated to cCMV related sequelae. No age weighting or time discounting was undertaken in line with current practices [18]. DALYs for a given pathogen were obtained by summing the DALYs for each of the causally related health states. DALYs were calculated for reference year 2013, using birth and fetal death estimates from the Scientific Institute of Public Health, and were also expressed per 100

000 population in Belgium. In 2013, the total number of live births was 125 606 among a population of about 11.2 million people in Belgium [17].

Statistical analyses

If more than two studies were found, quantitative data were summarized into a single estimate through a random effects meta-analysis in a Bayesian framework using a binomial likelihood [8,20]. If only two studies were found, they were combined in a uniform distribution. Probabilistic sensitivity analysis was used to propagate the uncertainty in the input parameters to the final DALY estimate, based on 1 000 000 Monte Carlo simulations. Supplementary appendix 2 and 3 show the data and distributions used to estimate the health burden. All parameters were summarized by their mean and a 95% uncertainty interval (UI) defined as the 2.5^{th} and 97.5^{th} percentile. To show the contribution of each variable to the overall uncertainty of the end result variable importance analyses based on partial correlation coefficients were conducted. Data management was done in Microsoft Excel 2010 and all calculations were performed in R 3.2.0 [21].

Results

Out of 454 unique citations, 12 studies were eligible for inclusion in the analysis of the seroprevalence and incidence of cCMV and CT in Belgium (Fig. 1).

Congenital toxoplasmosis

Two studies were found concerning *T. gondii* seroprevalence in pregnant women but without any specification of age. The seroprevalence ranged from 49 to 50% and the sample size from 784 to 16 541 [22, 23]. A uniform distribution on this range yielded a mean seroprevalence of toxoplasmosis in pregnant women of 50% (UI: 49–50).

No reports were found concerning the incidence of congenital toxoplasmosis in Belgium. Two papers published in the period 1995–2015, included data on seroconversions among pregnant women in Belgium [22, 23]. A uniform distribution, with the study results from Breugelmans et al. [22] and Layasu et al. [23] as the minimum and maximum estimates, respectively, resulted in a seroconversion rate of 0.22% (UI: 0.06–0.37). Our random effects meta-analysis on the data from the review by Torgerson & Mastroiacovo [12] yielded a mean rate of maternal-to-fetal transmission following primary infection of 25% (UI: 18–33). Multiplying this with the seroconversion rate in pregnant women resulted in a CT incidence of 5.5 per 10 000 fetuses (UI: 1.4–10). This means that in 2013 in Belgium 69 infants (UI: 18–131) were estimated to be born with CT.

We estimated a public health impact of 188 DALYs (UI: 43–419) in Belgium, consisting of 147 YLDs (UI: 32–344) and 41 YLLs (UI: 8.7–98) (Table 1). The uncertainty in the estimate of the seroconversion rate had the greatest impact on the DALY estimate (Fig. 2).

To explore the impact of assumptions, different scenarios were analyzed on the impact of fetal death and different prevention measures (based on additional papers published <1995) (Fig. 3): 1) CT, the scenario explained above; 2) CT+FD: scenario 1 accounting for fetal loss ≥ 22 weeks gestation, which increases the impact by 206 (UI: 93-342) YLL; 3) CT comprehensive prevention (Full_prev): a scenario based on the seroconversion rate published in a study (1991–2001), in which a comprehensive prevention campaign was conducted [22]; 4) CT medium prevention (Med_prev): in which we used a study (1983–1990) where seronegative pregnant women received a written list of recommendations on primary prevention [24]; and 5) CT no prevention (No_prev): a scenario in which women received no information about primary prevention (1979–1982) [25]. We also included the impact of fetal death in the latter three scenarios.

A comprehensive overview of all data used, summary measures and methodology is given in Supplementary appendix 2.

Cytomegalovirus infection

Seven studies concerning CMV seroprevalence in women of childbearing age were selected from the publications within the period 1995–2015 [1,26,27,28,29,30,31]. The seroprevalence ranged from 28 to 57% and the sample size from 126 to 7140. A random-effects meta-analysis showed a seroprevalence of CMV infection in women of childbearing age of 41% (UI: 28–55).

Only one source addressed the incidence of cCMV infection in Belgium based on universal screening of newborns [32]. Based on this study we estimated a cCMV birth prevalence of 52 per 10 000 live births in Belgium (UI: 41–64), which means that 651 children (UI: 516–802) were estimated to be born with cCMV infection in 2013.

Our random effects meta-analysis on cCMV related sequelae from the systematic review by Dollard et al. [13] showed that 11% (UI: 6.5–16) of all infants born with cCMV infection are symptomatic at birth. This means that in Belgium 70 cCMV infected infants (UI: 40–109) were symptomatic at birth and 581 (UI: 457–720) asymptomatic at birth. Of all infants symptomatic at birth approximately 73% (UI: 31–99) (n=51 [UI: 18–91]) had permanent sequelae, but infants that were asymptomatic at birth developed sequelae as well (12% [UI: 5.4–20]; n=68 [UI: 30–121]). This means 18% (UI: 11–27) of cCMV infected children had life-long sequelae. The meta-analysis showed that cCMV related hearing loss occurs at a median age of 1.0 (UI: 0.1–2.9) months in children symptomatic at birth and at 6.0 (UI: 0–36) months in children asymptomatic at birth.

Based on the available information we estimated a public health impact of 1032 (UI: 226–2820) and 944 (UI: 317–1970) DALYs in children symptomatic and asymptomatic at birth,

153 respectively. The total public health impact was 1976 DALYs (UI: 757–4067) in Belgium in
154 2013, which consisted of 1839 YLDs (UI: 671–3886) and 137 YLLs (UI: 0–654) (Table 2).
155 The variable importance analysis showed that especially the uncertainty in the estimate of the
156 proportion of children symptomatic at birth with SNHL and MD had a great impact on the
157 DALY estimate (Fig. 4).

158 We explored the impact of the inclusion of fetal loss and visual impairment (Fig. 5). Scenario
159 1 (cCMV) consisted of the results explained above. Scenario 2 (cCMV+CR) explored the
160 impact of including data on chorioretinitis, which increased the impact by 38 YLD (UI: 7.6–
161 116) [34]. Scenario 3 (cCMV+CR+FD) included both chorioretinitis and fetal loss, in which
162 the latter increases the impact by 2545 YLL (UI: 313–7011) [1,34].

163 An overview of the data used, summary measures and methodology is given in
164 Supplementary appendix 3.

165 ## Discussion

166 We updated the burden estimation for CT to the most recent DWs, and, to our knowledge
167 performed the first DALY assessment of cCMV. We used a “best available evidence”
168 approach to integrate disparate data sources and propagate related uncertainties. Not all
169 required information was available: no age-stratified seroprevalence reports were available
170 that suited our inclusion criteria, while available information does not provide an accurate
171 representation of Belgium (i.e., overrepresentation of the Brussels area and
172 underrepresentation of the Walloon region) and differences in seroprevalence can be seen
173 across the different regions.

174 Our analysis could not account for time-specific changes in infection rates, which may have
175 induced an overestimation of the current incidence of both congenital infections. Since we

176 only included studies within the reasonably short period 1995-2015, this influence may not be
177 very large.

178 Only few data are available in Belgium about CT and cCMV related sequelae and their onset.
179 Since cCMV related sequelae and their onset do not seem to differ between countries we used
180 available data from different studies to increase the accuracy of our estimates. The CT data
181 we used are consistent with the CT sequelae reported when predominantly type 2 genotypes
182 are involved, as seen in Europe [35]. However, clinical terms used to describe sequelae in the
183 literature and the methods used to measure sequelae were not always clearly defined or
184 standardized across studies. Not all studies were equally thorough in ascertaining the different
185 sequelae, standardized data on visual impairment due to cCMV and intra-uterine and perinatal
186 mortality and pregnancy termination were lacking, and the follow-up of infected children has
187 been too short to fully identify late-onset sequelae, which might have lead to underestimation
188 of the burden [13].

189 We estimated a public health impact of 188 DALYs (UI: 43–419) for CT in Belgium in 2013.
190 This is lower than the burden reported in the Netherlands (2303 DALYs, with a range of 818–
191 6713) [11], noting that this was estimated based on an annual 194 000 live-born babies in
192 comparison to 125 606 in Belgium and fetal loss was included in this estimate. However, our
193 estimate is still lower when we included fetal loss (394 DALYs [UI: 188–657]). Since the
194 same rate of occurrence and duration of sequelae were used for these estimations and the
195 updated DWs of sequelae were not very different from earlier studies, the discrepancy is due
196 to differences in the number of births, CT incidence estimates and the exclusion of fetal loss
197 in our study. Our lower CT incidence estimate (5.5 per 10 000 fetuses [UI: 1.4–10]) compared
198 to 20 per 10 000 live births in the Netherlands [11]) can be explained by the use of data on
199 seroconversions from two studies, including one where comprehensive primary prevention

measures were implemented [22,23]. Important to note here is that the scenario analysis clearly shows that prevention measures can have an important impact on the burden, although we cannot rule out a time effect. In addition, seroconversion was defined as no *T. gondii* IgG antibodies in the first serum sample but development of IgG antibodies in a subsequent sample, which means the seroconversion rate might have been underestimated. Finally, the higher seroprevalence in pregnant women in Belgium (50% compared to 33% in the Netherlands [11]) might imply a reduced risk of toxoplasmosis during pregnancy.

Torgerson & Mastroiacovo [12] estimated a public health impact in Belgium of 230 DALYs (95% credible interval (CI): 67–516) including fetal loss. In the Europe A region a public health impact of 2.8 DALYs per 1 000 live births (UI: 1.3-4.3) was reported [12], which is higher than our estimate for Belgium with 1.5 (UI: 0.3-3.3) DALYs per 1 000 live births. The main differences with our results lay in the CT incidence estimates and inclusion of fetal loss.

The results in the present study provide the first estimation of the public health impact of cCMV in terms of DALYs, and found it to be higher than CT in Belgium (1976 DALYs (UI: 757–4067) DALYs). Sequelae (other than SNHL [34]) could be relatively less severe for the asymptomatic children at birth so we might have overestimated the DALYs in this group. Primary prevention has also shown to result in reductions in CMV seroconversions [36,37]. However, due to a lack of data on the impact of prevention on the incidence of cCMV resulting from both primary and recurrent CMV infections during pregnancy we were not able to produce reliable DALY estimates for a scenario representing the impact of prevention.

Including data on fetal loss would considerably increase the DALY estimates for both CT and cCMV. Therefore, the DALY estimates associated with both congenital infections are likely underestimates. The data show that to a lesser extent CT but especially cCMV are important but currently under recognized clinical and public health problems. De Vries et al. [38]

estimated that it is more common than several disorders included in newborn screening. A burden of 21.8 (17.2-26.8) DALY per 100 000 population was estimated for Down syndrome in Belgium in 2015 [39], which is comparable to our cCMV burden estimate.

Because the above mentioned existing data gaps, an accurate and representative estimation of the current true impact of congenital infections in Belgium could not be extracted from literature alone. Therefore, it could help if future studies would identify congenitally infected children through universal screening, standardize, clearly define and include all sequelae and extend the follow-up. In addition, it is recommended to include information on intra-uterine and perinatal mortality and pregnancy termination. Furthermore, a control group should be included in each study to control bias. In Belgium, it is furthermore important to estimate the true incidence of both congenital infections based on existing routine data sources in addition to the literature.

Conclusion

CT and especially cCMV infection are serious infections that have an important impact on Belgian public health, although several data gaps remain. The scenario analysis showed important increases in DALYs when fetal losses were included and decreases when comprehensive CT prevention measures were conducted. Our results and identified data gaps may increase awareness and support decisions regarding public health policy and interventions. Similar studies in other countries may stimulate public health interventions against these diseases.

Funding

This work was supported by the Research Foundation – Flanders (FWO Aspirant), Brussels, Belgium. NH gratefully acknowledges support from the University of Antwerp scientific chair in Evidence-Based Vaccinology, financed in 2009–2016 by a gift from Pfizer and in 2016 from GSK. The funding bodies have no role in the design of the study, and the collection, analysis and interpretation of data and in writing the manuscript.

Conflict of interest

The authors have no competing interests.

References

1. Naessens A, Casteels A, Decatte L, Foulon W. A serologic strategy for detecting neonates at risk for congenital cytomegalovirus infection. J Pediatr, **2005**; 146: 194-7.

2. Vanhaesebrouck P, Foulon W, Van Renterghem L, Goossens L, Temmerman M. Perinatale *Toxoplasma gondii*-infectie: Een update anno 2002. Tijdschr Geneeskd, **2003**; 59: 663-71.

3. Del Pizzo J. Focus on diagnosis: congenital infections (TORCH). Pediatr Rev, **2011**; 32: 537-42.

4. Carlier Y, Truyens C, Deloron P, Peyron F. Congenital parasitic infections: a review. Acta Trop, **2012**; 121: 55-70.

5. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev, **2013**; 26: 86-102.

6. Gyselaers W, Jonckheer P, Ahmadzai N, *et al*. What are the recommended clinical assessment and screening tests during pregnancy? Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 248. D/2015/10.273/58.

Available at:
https://kce.fgov.be/sites/default/files/page_documents/KCE_248_assessments_and_test_during_pregnancy_Report_0.pdf. Accessed 27 Aug 2016.

7. Thiébaut R, Leproust S, Chêne G, Gilbert R; SYROCOT. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. Lancet, **2007**; 369: 115-22.

8. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, PLoS Med. **2009**; 6:e1000097.

9. Devleesschauwer B, Havelaar AH, Maertens de Noordhout C, *et al*. DALY calculation in practice: a step-wise approach. Int J Public Health, **2014**; Jun;59(3): 571-4.

10. Havelaar AH, Kemmeren JM, Kortbeek LM. Disease burden of congenital toxoplasmosis. Clin Infect Dis, **2007**; 44: 1467-74.

11. Kortbeek LM, Hofhuis A, Nijhuis CDM, Havelaar AH. Congenital toxoplasmosis and DALYs in the Netherlands. Mem Inst Oswaldo Cruz, **2009**; 104(2): 370-373.

12. Torgerson PR and Mastroiacovo P. The global burden of toxoplasmosis: a systematic review. Bull World Health Organ, **2013**; 91: 501–508.

13. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol, **2007**; 17: 355-63.

14. Foulon I, Naessens A, Faron G, Foulon W, Jansen AC, Gordts F. Hearing thresholds in children with a congenital CMV infection: A prospective study. Int J of Pediatr Otorhinolaryngol, **2012**; 76: 712–717.

290 15. Royackers L, Rector E, Verhaert N, Desloovere C. Long-term audiological follow-up
291 of children with congenital cytomegalovirus. B-ENT, **2013**; 9(suppl 21): 57–64.

292 16. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal
293 investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad
294 Audiol, **2000**; 11(5): 283–290.

295 17. SPMA , Public Health and Surveillance (2016). Scientific Institute of Public Health,
296 Brussels, Belgium. Available at: https://spma.wiv-isp.be/. Accessed 27 Aug 2016.

297 18. Murray CJ, Ezzati M, Flaxman AD, *et al*. GBD 2010: design, definitions, and metrics.
298 Lancet, **2012**; 380: 2063–2066. doi: 10.1016/S0140-6736(12)61899-6.

299 19. Salomon JA, Haagsma JA, Davis A, *et al*. Disability weights for the Global Burden of
300 Disease 2013 Study. Lancet Glob Health, **2015**; 3: e712-23.

301 20. Devleesschauwer B, Ale A, Torgerson P, *et al*. The burden of parasitic zoonoses in
302 Nepal: A systematic review. PLoS Negl Trop Dis, **2014**; 8(1):e2634. Doi:
303 10.1371/journal.pntd.0002634.

304 21. R Core Team (2015). R: A language and environment for statistical computing. R
305 Foundation for Statistical Computing, Vienna, Austria. URL: http://www.R-project.org/.

306 22. Breugelmans M, Naessens A, Foulon W. Prevention of toxoplasmosis during
307 pregnancy - an epidemiologic survey over 22 consecutive years. J perinat. Med, **2004**; 32:
308 211-214.

309 23. Luyasu V, Robert A, Lissenko D, *et al*. A seroepidemiological study on
310 toxoplasmosis. Acta Clin Belg, **1997**; 52(2): 68.

311 24. Foulon W, Naessens A, Derde MP: Evaluation of the possibilities for preventing
312 congenital toxoplasmosis. Am J Perinatol, **1994**; 11: 57.

313 25. Foulon W, Naessens A, Volckaert M, Lauwers S, Amy JJ. Congenital toxoplasmosis:
314 a prospective survey in Brussels. Br J Obstet Gynaecol, **1984**; 91: 419.

315 26. De Schryver A, De Bacquer D, Van Renterghem L, De Henauw S, De Backer G.
316 Epidemiology of cytomegalovirus in Belgium. Arch Public Health, **1997**; 55(1): 59.

317 27. Donders G. Surveillance of infection during pregnancy: the boundary between routine
318 screening and symptom-driven diagnosis [dissertation]. Leuven, Belgium, 1997 (as cited in
319 Kiss et al., 2002).

320 28. Francisse S, Revelard P, De Maertelaer V, Strebelle E, Englert Y, Liesnard C. Human
321 cytomegalovirus seroprevalence and risk of seroconversion in a fertility clinic population.
322 Obstet Gynaecol, **2009**; 114(2): 285-291.

323 29. Kiss P, De Bacquer D, Sergooris L, De Meester M, Vanhoorne M. Cytomegalovirus
324 Infection: An Occupational Hazard to Kindergarten Teachers Working with Children Aged
325 2.5–6 Years. Int J Occup Environ Health, **2002**; 8: 79-86.

326 30. Leuridan E, Ieven M, Hens N, Van Damme P. High susceptibility to cytomegalovirus
327 infection of pregnant women in Flanders, Belgium. FVV in ObGyn*,* **2012**; 4(2): 76-81.

328 31. Liesnard CA, Revelard P, Englert Y. Is matching between women and semen donors
329 feasible to avoid cytomagalovirus infection in artificial insemination with donor semen? Hum
330 Reprod*,* **1998**; 13(2): 25-31.

331 32. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. Hearing loss in children with
332 congenital cytomegalovirus infection in relation to the maternal trimester in which the
333 maternal primary infection occurred. Pediatrics, **2008**; 122(6): e1123-e1127.

33. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooghe I. Hearing loss and congenital CMV infection: a systematic review. Pediatrics, **2014**; 134: 972-982.

34. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med, **1992**; 326(10): 663-667.

35. Ajzenberg D, Cogné N, Paris L*, et al*. Genotype of 86 Toxoplasma gondii isolates associated with human congenital toxoplasmosis, and correlation with clinical findings. J Infect Dis, **2002**; 186: 684–689.

36. Revello MG, Tibaldi C, Masuelli G, *et al.* The CCPE Study Group. Prevention of primary cytomegalovirus infection in pregnancy. EBioMedicine, **2015;** 2: 1205–1210.

37. Vauloup-Fellous C, Picone O, Cordier AG, *et al*. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. J Clin Virol, **2009;** 46: S49–S53.

38. de Vries JJ, Vossen AC, Kroes AC, van der Zeijst BA. Implementing neonatal screening for congenital cytomegalovirus: addressing the deafness of policy makers. Rev Med Virol, **2011**; 21: 54-61.

39. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2016. Available from http://vizhub.healthdata.org/gbd-compare. Accessed 24 Feb 2017

Table Legends

Table 1. Incidence, duration, disability weights and disease burden of the various sequelae associated with congenital toxoplasmosis

Abbreviations: UI, uncertainty interval; DALYs, disability adjusted life years; CNS, central nervous system.

[a] Data were adapted from Havelaar et al. [10], Kortbeek et al. [11], Torgerson & Mastroiacovo [12] and Salomon et al. [19].

[b] Adapted from the Belgian life expectancy table for 2012 [17].

[c] Moderate distance vision impairment.

[d] Uniform distribution of no to mild motor and cognitive impairments.

[e] PERT distribution with lower limit of profound intellectual disability (min) and upper limit of severe motor impairment (max) and the weighted mean of one case with severe motor impairment and two cases with profound intellectual disability as most likely estimate (mode).

[f] Uniform distribution of mild to severe motor and cognitive impairments

Table 2. Incidence, duration, disability weights and disease burden of the various sequelae associated with congenital cytomegalovirus infection

Abbreviations: UI, uncertainty interval.

[a] Data were adapted from the systematic review by Dollard et al. [13].

[b] Adapted from the Belgian life expectancy table for 2012 [17].

[c] Data were adapted from the systematic review by Salomon et al. [19].

[d] Hearing loss: 77% of cases with hearing loss have severe to profound hearing loss [33], therefore we used a PERT distribution from mild (min) to complete (max) hearing loss with severe to profound hearing loss as most likely estimate (mode).

[e] Disability weights uniform from mild to profound.

[f] Disability weight of comorbidity: $1 - (1 - DW_A)(1 - DW_B)$.

Figure legends

Fig 1. Flowchart showing study selection for the systematic review of recent literature on the seroprevalence and incidence of toxoplasmosis and cytomegalovirus infections in women of childbearing age and the incidence of both congenital infections in Belgium.

Fig 2. Variable importance analysis indicating which parameters influence the DALY estimate for congenital toxoplasmosis in Belgium.

The partial correlations coefficients show the impact of the different uncertain parameters on the uncertainty of the overall estimates.

Abbreviations: DW, disability weight; HC, hydrocephalus; LOCR, late onset chorioretinitis; CNS, central nervous system abnormalities; ND, neonatal death; IC, intracranial calcifications; CR, chorioretinitis before the age of one year.

Fig 3. Bar plot of the results of 5 scenarios examining the public health impact of congenital toxoplasmosis.

Abbreviations: CT, the scenario explained in this study; CT+FD, the scenario accounting for fetal loss ≥ 22 weeks gestation; (Full_prev): a scenario based on the seroconversion rate published in a study, in which a comprehensive prevention campaign was conducted [22]; Med_prev: in which we used a study where seronegative pregnant women received a written list of recommendations on primary prevention [24]; No_prev: a scenario in which women received no information about primary prevention [25]. We also included the impact of fetal death in the latter three scenarios; yld, years lived with disability; yll_ND, years of life lost due to neonatal death; yll_FD, years of life lost due to fetal loss.

Fig 4. Variable importance analysis indicating which parameters influence the DALY estimate for congenital cytomegalovirus infection in Belgium.

The partial correlations coefficients show the impact of the different uncertain parameters on the uncertainty of the overall estimates.

Abbreviations: SNHL, sensorineural hearing loss; MD, motor deficit; DW, disability weight; CD, cognitive deficit; cCMV, congenital cytomegalovirus infection; ND, neonatal death.

Fig 5. Bar plot of the results of 3 scenarios examining the public health impact of congenital cytomegalovirus infection.

Abbreviations: cCMV: the scenario explained in this study; cCMV+CR: the scenario including chorioretinitis; cCMV+FD+CR: the scenario including chorioretinitis and fetal loss; yld, years lived with disability; yll_ND, years of life lost due to neonatal death; yll_FD, years of life lost due to fetal loss.

Table 1. Incidence, duration, disability weights and disease burden of the various sequelae associated with congenital toxoplasmosis

Sequela	Incidence[a] per 100 cases (95%UI)	Duration (years)[b]	Disability weight[a]	DALYs per year (95%UI)	DALYs per 100 000 population (95%UI)
Chorioretinitis later in life	16 (5-52)	70.65	0.031 (0.019-0.049)[c]	24 (0.4-100)	0.22 (0.004-0.9)
Chorioretinitis in first year of life	13 (12-15)	80.25	0.031 (0.019-0.049)[c]	22 (4.9-50)	0.20 (0.04-0.5)
Intracranial calcifications	11 (7.9-12)	80.25	0.025 (0.001-0.049)[d]	15 (0.6-45)	0.14 (0.005-0.4)
CNS abnormalities	2.9 (1.0-6.0)	80.25	0.291 (0.165-0.447)[e]	46 (6.7-138)	0.42 (0.06-1.2)
Hydrocephalus	2.0 (1.0-3.0)	80.25	0.360 (0.035-0.685)[f]	40 (2.6-123)	0.35 (0.02-1.1)
Neonatal death	0.7 (0.4-1.2)	80.25	1	41 (8.7-98)	0.37 (0.1-0.9)
Total YLD				**147 (32-344)**	**1.3 (0.3-3.1)**
Total YLL				**41 (8.7-98)**	**0.37 (0.1-0.9)**
Total DALYs				**188 (43-419)**	**1.7 (0.4-3.8)**

Abbreviations: UI, uncertainty interval; DALYs, disability adjusted life years; CNS, central nervous system.

[a] Data were adapted from Havelaar et al. [10], Kortbeek et al. [11], Torgerson & Mastroiacovo [12] and Salomon et al. [19].

[b] Adapted from the Belgian life expectancy table for 2012 [17].

[c] Moderate distance vision impairment.

[d] Uniform distribution of no to mild motor and cognitive impairments.

[e] PERT distribution with lower limit of profound intellectual disability (min) and upper limit of severe motor impairment (max) and the weighted mean of one case with severe motor impairment and two cases with profound intellectual disability as most likely estimate (mode).

[f] Uniform distribution of mild to severe motor and cognitive impairments

Table 2. Incidence, duration, disability weights and disease burden of the various sequelae associated with congenital cytomegalovirus infection

Syndrome	Incidence per 100 cases[a] (95% UI)		Incidence per year[a] (95% UI)		Duration[b] (years)	Disability weight[c] (95% UI)	DALY per year (95% UI)	DALY per 100 000 population (95% UI)
	Symptomatic at birth	Asymptomatic at birth	Symptomatic at birth	Asymptomatic at birth				
Sensorineural hearing loss in symptomatic cases	17 (1.7-49)		12 (1.1-37)		80.19 (80.08-80.24)	0.173 (0.061-0.274)[d]	164 (12-564)	1.5 (0.1-5.0)
Sensorineural hearing loss in asymptomatic cases		7.4 (2.6-14)		43 (15-86)	79.85 (77.58-80.25)	0.173 (0.061-0.274)[d]	591 (132-1394)	5.3 (1.2-13)
Cognitive deficit	18 (1.7-53)	1.0 (0-3.8)	12 (1.1-39)	5.9 (0.01- 22)	80.25	0.155 (0.032-0.277)[e]	226 (21-752)	2.0 (0.2-6.7)
Sensorineural hearing loss	7.3 (0.02-30)	0.3 (0-1.3)	5.2 (0.01-22)	1.6 (0-7.6)	80.25	0.301	163 (7.0-619)	1.5 (0.06-5.5)

+ cognitive deficit						(0.144-0.439)[f]		
Sensorineural hearing loss + motor deficit	18 (0.1-68)	0	13 (0.08-50)	0	80.25	0.400 (0.150-0.624)[f]	413 (2.4-1726)	3.7 (0.02-15)
Cognitive deficit + motor deficit	8.8 (0-47)	0.6 (0.01-2.3)	6.1 (0-34)	3.6 (0.08-13)	80.25	0.360 (0.035-0.685)[e]	282 (7.0-1292)	2.5 (0.06-12)
Neonatal death	0	0.3 (0-1.3)	0	1.6 (0-7.6)	80.25	1	137 (0-654)	1.2 (0-5.9)
Total YLD							**1839 (671-3886)**	**17 (6-35)**
Total YLL							**137 (0-654)**	**1.2 (0-5.9)**
Total DALYs							**1976 (757-4067)**	**18 (6.8-36)**

Abbreviations: UI, uncertainty interval.

[a] Data were adapted from the systematic review by Dollard et al. [13].

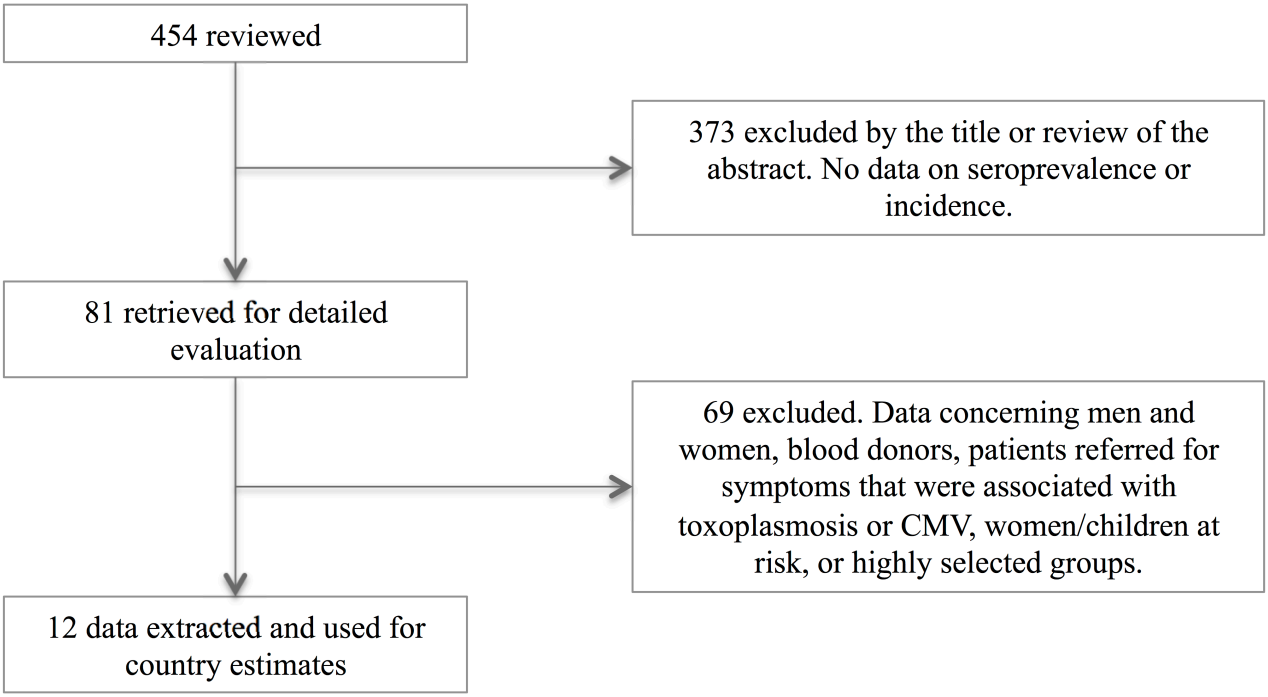
[b] Adapted from the Belgian life expectancy table for 2012 [17].

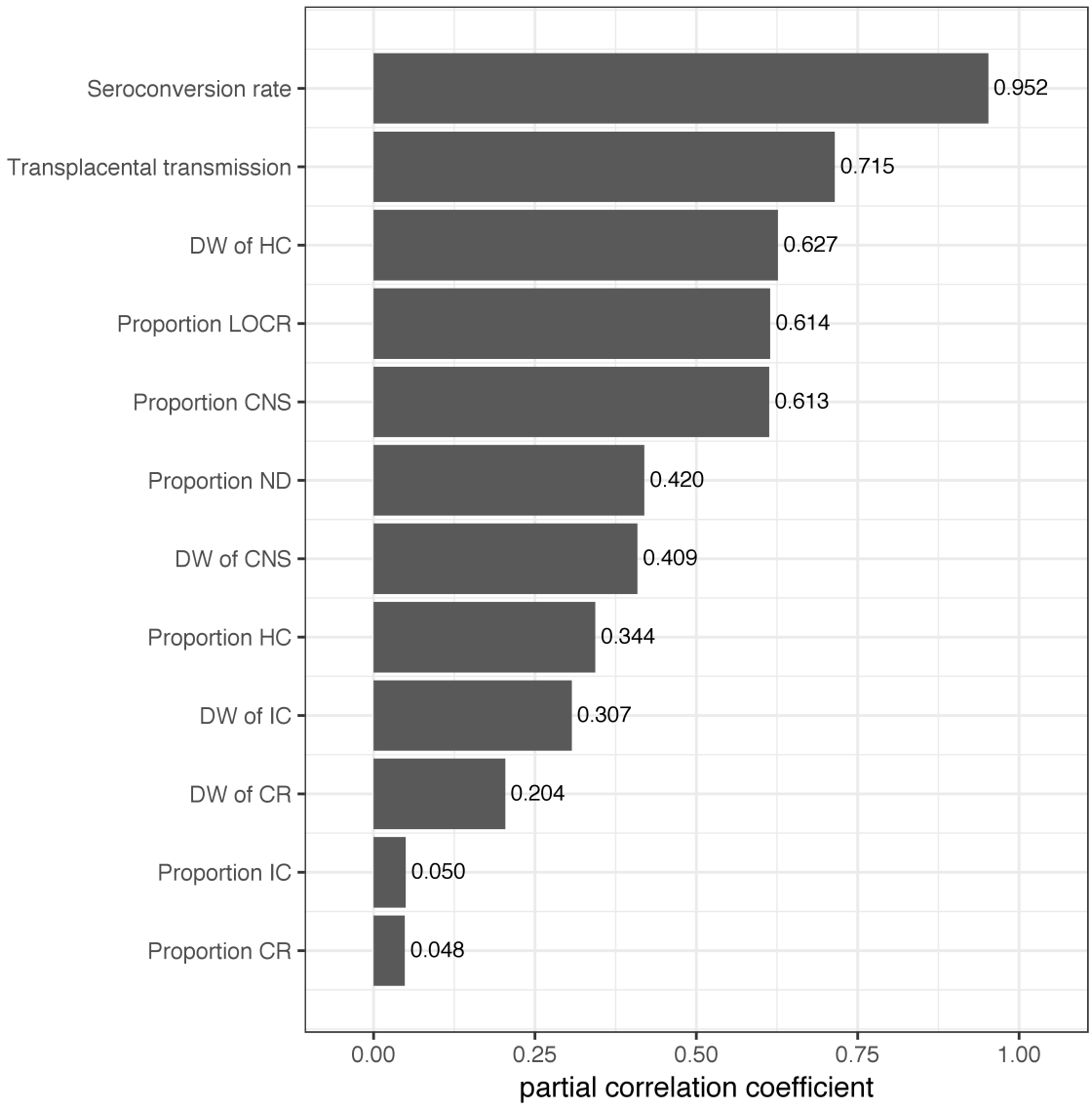
[c] Data were adapted from Salomon et al. [19].

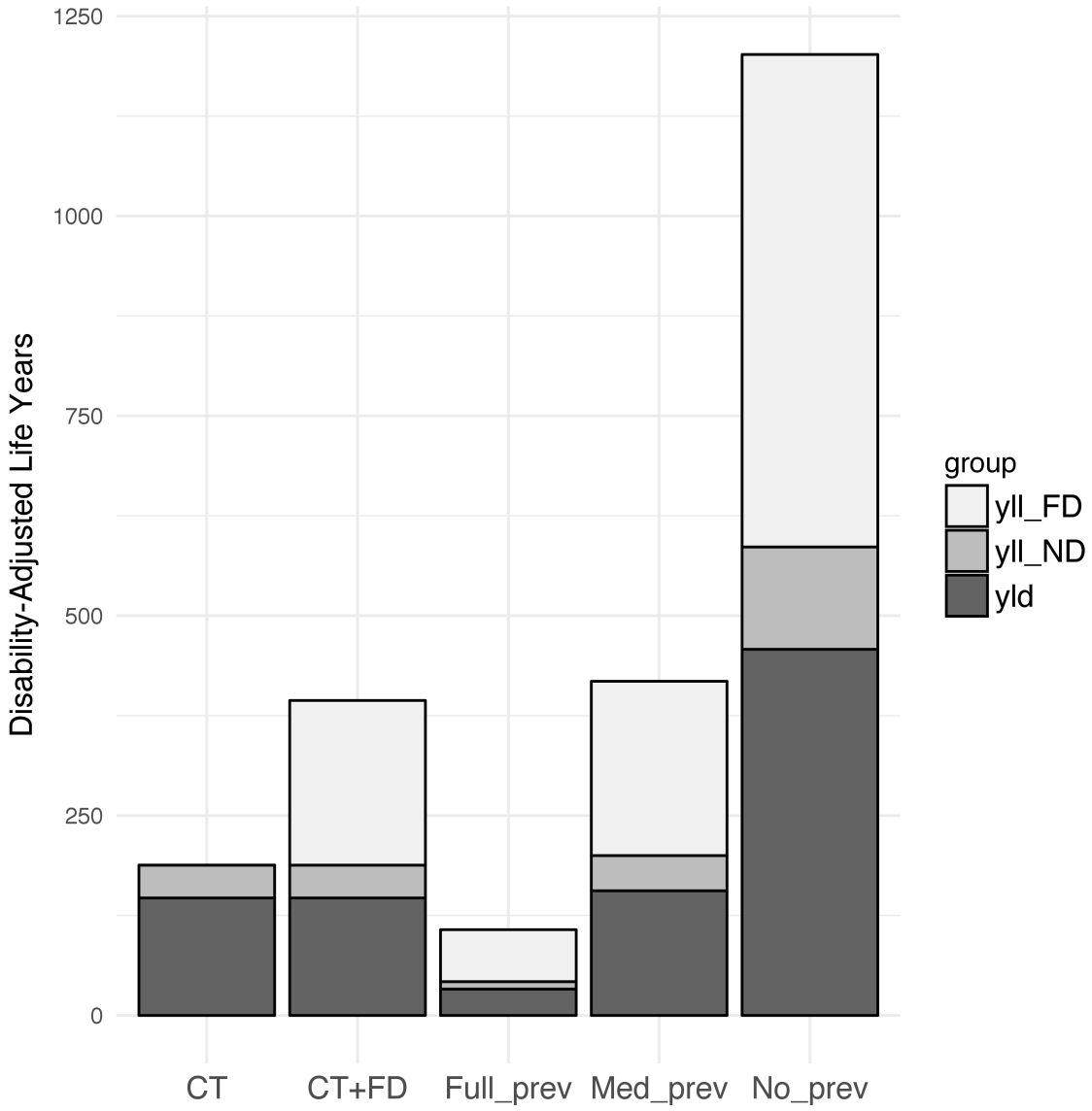
[d] Hearing loss: 77% of cases with hearing loss have severe to profound hearing loss [33], therefore we used a PERT distribution from mild (min) to complete (max) hearing loss with severe to profound hearing loss as most likely estimate (mode).

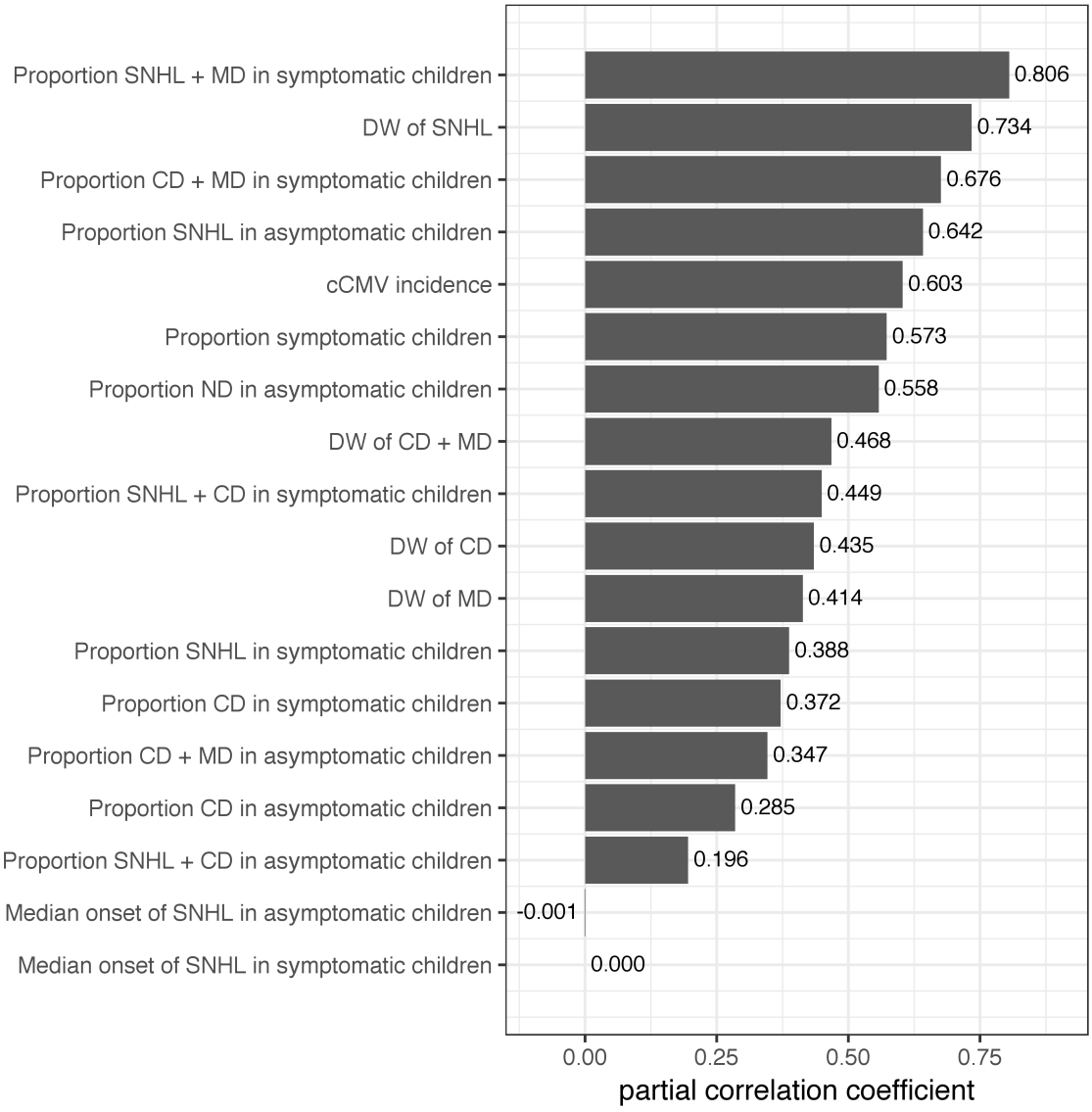
[e] Disability weights uniform from mild to profound.

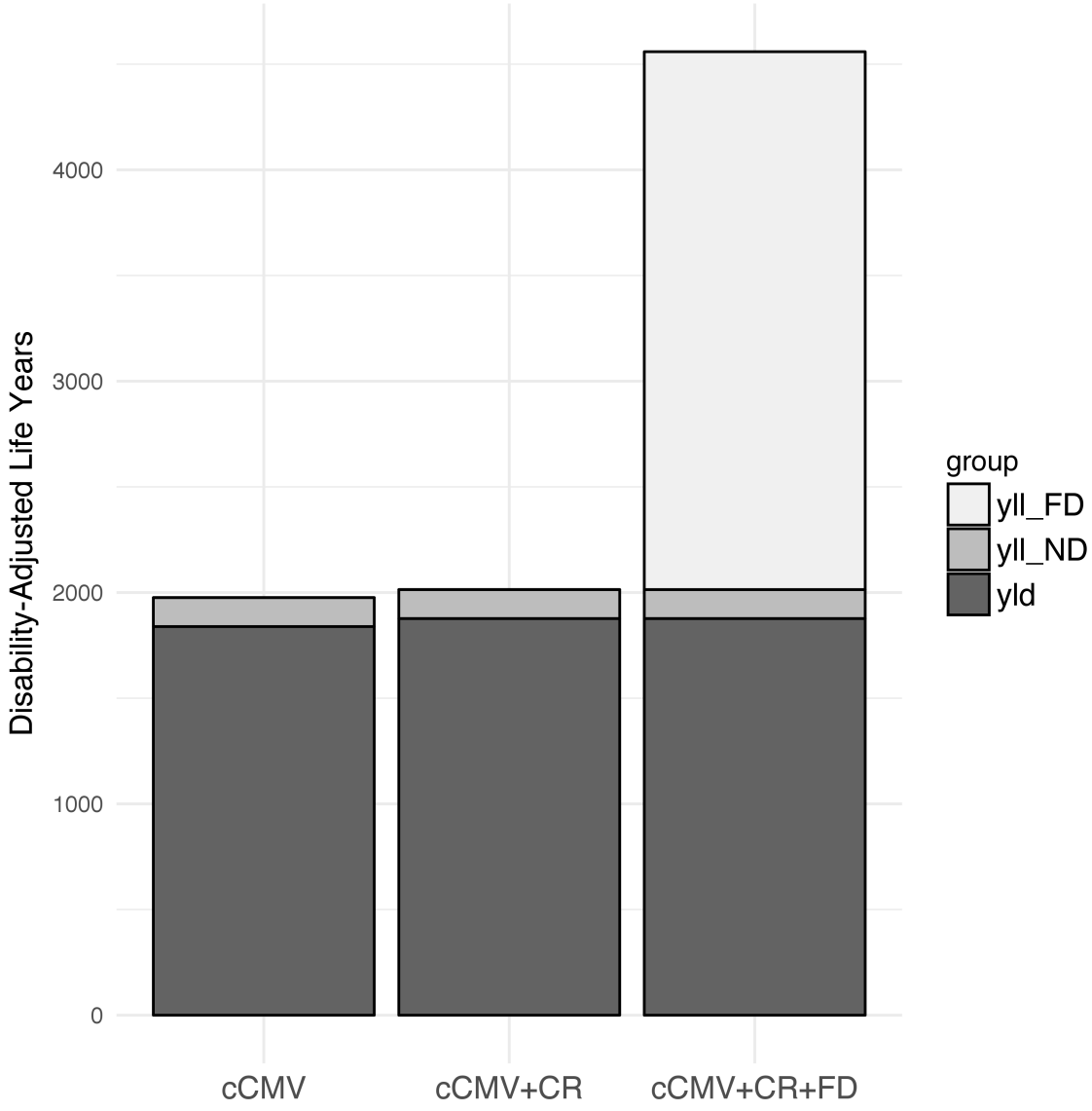
[f] Disability weight of comorbidity: $1 - (1 - DW_A)(1 - DW_B)$


454 reviewed
373 excluded by the title or review of the abstract. No data on seroprevalence or incidence.
81 retrieved for detailed evaluation
69 excluded. Data concerning men and women, blood donors, patients referred for symptoms that were associated with toxoplasmosis or CMV, women/children at risk, or highly selected groups.
12 data extracted and used for country estimates


Seroconversion rate
Transplacental transmission
DW of HC
Proportion LOCR
Proportion CNS
Proportion ND
DW of CNS
Proportion HC
DW of IC
DW of CR
Proportion IC
Proportion CR
0.952
0.715
0.627
0.614
0.613
0.420
0.409
0.344
0.307
0.204
0.050
0.048
0.00
0.25
0.50
0.75
1.00
partial correlation coefficient


1250
1000
750
500
250
0
Disability-Adjusted Life Years
CT
CT+FD
Full_prev
Med_prev
No_prev
group
yll_FD
yll_ND
yld


Proportion SNHL + MD in symptomatic children
DW of SNHL
Proportion CD + MD in symptomatic children
Proportion SNHL in asymptomatic children
cCMV incidence
Proportion symptomatic children
Proportion ND in asymptomatic children
DW of CD + MD
Proportion SNHL + CD in symptomatic children
DW of CD
DW of MD
Proportion SNHL in symptomatic children
Proportion CD in symptomatic children
Proportion CD + MD in asymptomatic children
Proportion CD in asymptomatic children
Proportion SNHL + CD in asymptomatic children
Median onset of SNHL in asymptomatic children
Median onset of SNHL in symptomatic children
0.806
0.734
0.676
0.642
0.603
0.573
0.558
0.468
0.449
0.435
0.414
0.388
0.372
0.347
0.285
0.196
-0.001
0.000
0.00
0.25
0.50
0.75
partial correlation coefficient


Disability-Adjusted Life Years
4000
3000
2000
1000
0
cCMV
cCMV+CR
cCMV+CR+FD
group
yll_FD
yll_ND
yld

Supplementary material to *The public health impact of congenital toxoplasmosis and cytomegalovirus infection in Belgium, 2013: a systematic review and data synthesis (CID/2017)*

Table of contents

Appendix 1 PRISMA 2009 Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	P 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	P 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	P 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	M&M P 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Available upon request
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	P 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	P 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P 5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P 4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P 5, Appendix 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P 6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P 6-7

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P 5-7, Appendix 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	P 6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2 and 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P 10-13, Appendix 1,
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	P 7-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	P 10-13, Appendix 1

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	P 8-10. Table 1 and 2, Fig. 2-5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P 10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P 10-13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P 10-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P 14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 [1]

For more information, visit: **www.prisma-statement.org**.

Note: Methodological quality assessment was conducted at the level of development of the systematic review protocol including the eligibility criteria; study selection based on the eligibility criteria; collection of data from the studies, including the methods used and limitations; quality differences were integrated in the analysis by using a random effect meta-analysis; different scenarios were compared; variable importance analyses were conducted; and finally we reflect on the quality of the data in the discussion. Our predefined eligibility criteria were selected in such a way that selection bias could be detected and studies could be excluded if necessary. Detection bias was overcome by only selecting studies for Disability Adjusted Life Year (DALY) calculations where the diagnostic methods were described. Since we only used the number of cases found in the population tested from the different studies, other forms of bias were deemed unlikely.

Appendix 2 Congenital toxoplasmosis

Seroprevalence

Supplementary Table 1 shows the estimated summary measures and data elicited from studies published in the period 1995-2015 concerning the seroprevalence of toxoplasmosis in pregnant women in Belgium.

Supplementary Table 1. Studies published in the period 1995-2015 concerning the seroprevalence of toxoplasmosis in pregnant women in Belgium.

Reference	Study population	Seroprevalence % (95% CI)	n	pos	Timeframe	Region/Hospital	Comments
Luyasu et al., 1997 [2]	Pregnant women	50.3 (46.7-53.8)	784	394	1990	Brabant Walloon area and the South East of Brussels	
Breugelmans et al., 2004 [3]	Pregnant women	48.7 (47.9-49.4)	16541	8049	1991-2001	UZ Brussels	Prevention measures: Leaflet explaining toxoplasmosis as a disease, what measures could be taken to avoid toxoplasmosis during pregnancy. Reiteration of these recommendations during antenatal classes held around mid gestation.

Abbreviations: CI, confidence interval; n, sample size; pos, number of seropositive women; UZ Brussels, University Hospital Brussels.

Seroconversion

Supplementary Table 2 shows the estimated summary measures and data elicited from studies published in the period 1995-2015 concerning toxoplasmosis seroconversions in pregnant women in Belgium. In the studies from Brussels University Hospital different prevention measures were used and studies were separated in time (including two additional papers published <1995) [3,4,5].

Supplementary Table 2. Studies concerning toxoplasmosis seroconversions in pregnant women in Belgium.

Reference	Study population	Seroconversion rate % (95% CI)	n	pos	Seroconv[a]	Timeframe	Region/ Hospital	Prevention measures
Luyasu et al., 1997 [2]	Pregnant women	0.38 (0.079-1.1)	784	394	3[a]	1990	Brabant Walloon area and the South East of Brussels	Prevention measures recommended to pregnant women but details unknown. The authors suggest in their discussion that the preventive measures in the study region were probably ineffective.
Breugelmans et al., 2004 [3]	Pregnant women	0.048 (0.021-0.095)	16541	8049	8[b]	1991-2001	UZ Brussels	Leaflet explaining toxoplasmosis as a disease, what measures could be taken to avoid toxoplasmosis during pregnancy. Reiteration of these recommendations during antenatal classes held around mid gestation.
Foulon et al., 1994 [4]	Pregnant women	0.23 (0.14-0.36)	8300	4695	19[b]	1983-1990	UZ Brussels	Written list of recommendations on primary prevention
Foulon et al., 1984 [5]	Pregnant women	0.67 (0.41-1.0)	2986	1583	20[b]	1979-1982	UZ Brussels	No primary prevention

Abbreviations: CI, confidence interval; n, sample size; pos, number of seropositive women; seroconv, number of seroconversions during pregnancy; UZ Brussels, Brussels University Hospital.

[a] Detection method: IgG and IgM, when seronegative or when an equivocal immunity was found, serological controls were undertaken at regular intervals, either monthly or every two months, and at childbirth a final control was performed to detect any possible late seroconversion.

[b] Detection method: IgG and IgM at first prenatal visit, when seronegative retest at 20th week, 30th week and on cord blood during delivery. Seroconversion is defined as no toxoplasma IgG antibodies in the first serum sample but development of IgG antibodies in a subsequent sample or in cord blood.

The estimated Belgian toxoplasmosis seroconversion rate was used to estimate the incidence of congenital toxoplasmosis (CT), by multiplying this with the estimated rate of trans-placental transfer of the pathogen based on data from the review by Torgerson & Mastroiacovo [6]. We assumed that the seroconversion rate is equal over the total duration of pregnancy.

Transmission

Table 3 shows the estimated summary measures and data elicited from studies concerning toxoplasmosis transmission rate from mother to the unborn child.

Supplementary Table 3. Studies concerning trans placental transmission of toxoplasmosis from mother to the unborn child (adapted from Torgerson and Mastroiacovo [6])

References	CT	Seroconversions	Transmission % (95% CI)
Antsaklis et al., 2002 [7]	11	93	11.8 (6.1-20)
Bessieres et al., 2001 [8]	57	165	34.6 (27-42)
Dunn et al., 1999 [9]	161	591	27.2 (24-31)
Jenum et al., 1998 [10]	11	47	23.4 (12-38)
Lebech et al., 1999 [11]	27	141	19.1 (13-27)
Robert-Gangneux et al., 1999 [12]	27	110	24.6 (17-34)
Romand et al., 2001 [13]	75	271	27.7 (22-33)
SYROCOT et al., 2007 [14]	507	1705	29.7 (28-32)
Wallon et al., 1999 [15]	506	1721	29.4 (27-32)
Wallon et al., 2004 [16]	358	1354	26.4 (24-29)

Abbreviations: CT, number of congenital toxoplasmosis cases; Seroconversions, number of seroconversions during pregnancy; CI, confidence interval.

Parameters

Supplementary Table 4 shows the parameters used to estimate the burden of CT in Belgium in 2013.

Supplementary Table 4. Parameters used to estimate the burden of congenital toxoplasmosis

Description	Value/Distribution/Method	Mean (95% UI)	Ref
Total population in Belgium in 2013	11178436		[17]
Number of live births in 2013	125606		[17]
Number of iterations	1000000		
Seroprevalence of toxoplasmosis in women of childbearing age	Uniform(0.487,0.503)	50% (49-50)	[2,3]
Toxoplasmosis seroconversion rate in women of childbearing age	Uniform(0.00048, 0.0038)	0.22% (0.06–0.37)	[2,3]
Transplacental transmission of toxoplasmosis	bREM	25% (18–33)	[6-16]

Incidence of CT in 2013	Seroconversion rate*transmission *number of live births	69 (18–131)	
Incidence of chorioretinitis later in life in CT cases	Beta(0.94, 4.9)	16% (5-52)	[6,18-19]
Incidence of chorioretinitis in first year of life in CT cases	Beta(243.3, 1628)	13% (12-15)	[6,18-19]
Incidence of intracranial calcifications in CT cases	Beta(107.1, 866.6)	11% (7.9-12)	[6,18-19]
Incidence of CNS abnormalities in CT cases	Beta(4.7, 158.0)	2.9% (1.0-6.0)	[6,18-19]
Incidence of hydrocephalus in CT cases	Beta(15.7, 770.7)	2.0% (1.0-3.0)	[6,18-19]
Incidence of neonatal mortality in CT cases	Beta(10.8, 1538)	0.7% (0.4-1.2)	[6,18-19]
DW chorioretinitis	Beta(15.1, 472.3)	0.031 (0.019-0.049)	[6,18-20]
DW intracranial calcifications	Uniform(0, 0.050)	0.025 (0.001-0.049)	[6,18-20]
DW CNS abnormalities	PERT(min=0.133, mode=0.268, max=0.545)	0.291 (0.165-0.447)	[6,18-20]
DW hydrocephalus	Uniform(0.018, 0.702)	0.360 (0.035-0.685)	[6,18-20]
DW neonatal or fetal mortality	1	1	[6,18-20]
Total number of fetal losses ≥22 weeks gestation in Belgium in 2013	571		[17]
Number of pregnancies ≥22 weeks in Belgium in 2013	125606 * (18/40) + 571	57094	
High estimate of CT related fetal loss incidence	Pregnancies * seroconversion rate * Beta(75, 1788)	5.0 (1.3-9.2)	[18, 21-24]
Most likely estimate of CT related fetal loss incidence	Pregnancies * seroconversion rate * Beta(47, 2629)	2.2 (0.6-4.2)	[18, 25]
Low estimate of CT related fetal loss incidence	Total number of fetal losses (≥22 weeks) in Belgium * 0.13%	0.74	[17, 18]
Incidence of fetal loss in CT cases	PERT(min=0.74, mode=2.2, max=5.0)	2.4 (1.1-4.0)	
Toxoplasmosis seroconversion rate in scenario with comprehensive prevention	Beta(8,16533)	0.05% (0.02-0.09)	[3]
Incidence of fetal loss in scenario with comprehensive prevention	PERT(min=0.49 mode=0.74, max=1.1)	0.8 (0.6- 1.0)	
Toxoplasmosis seroconversion rate in scenario with medium prevention	Beta(19, 8281)	0.23% (0.14-0.34)	[4]
Incidence of fetal loss in scenario with medium prevention	PERT(min=0.74, mode=2.3, max=5.3)	2.5 (1.1- 4.2)	
Toxoplasmosis seroconversion rate in scenario with minimum prevention	Beta(20, 2966)	0.67% (0.41- 1.0)	[5]
Incidence of fetal loss in scenario with minimum prevention	PERT(min=0.74, mode=6.7, max=15)	7.2 (2.3-13)	

Abbreviations: UI, uncertainty interval; Ref, reference; bREM, Bayesian random effect meta-analysis using a binomial likelihood [26]; CT, congenital toxoplasmosis; CNS, central nervous system; DW, disability weight; CI, credibility interval.

Scenario analyses

To explore the impact of assumptions, different scenarios were analyzed on the impact of fetal death and different prevention measures (based on additional papers published <1995) (Supplementary Fig. 1):

(1) CT: the baseline scenario as explained in the manuscript: based on the two papers, published in the period 1995–2015, which included data on seroconversions among pregnant women in Belgium [22, 23] and without accounting for fetal loss. In this scenario we estimated a public health impact of 188 Disability Adjusted Life Years (DALYs) (UI: 43–419) in Belgium, consisting of 147 Years Lived with Disability (YLDs) (UI: 32–344) and 41 Years of Life Lost (YLL) (UI: 8.7–98).

(2) CT with inclusion of fetal death (CT+FD): scenario 1 including accounting for fetal loss ≥ 22 weeks gestation. To calculate the incidence of CT related fetal loss in Belgium, we assessed the total number of pregnancies ≥22 weeks gestation in Belgium in 2013: 125 606 live-born children * (18/40) + 571 stillbirths at or after 22 weeks of gestation (national criteria, [17]). We multiplied this with the estimated seroconversion rate and the occurrence of fetal loss from Havelaar et al. [18], with a most likely 1.7%, and a maximum estimate of 4% fetal losses among seroconversions. The minimum estimate consisted of 0.13% fetal deaths due to toxoplasmosis [18], which we multiplied with the number of reported fetal deaths in Belgium ≥22 weeks of gestation (national criteria, [17]). We assumed that the seroconversion rate and the occurrence of fetal loss are equally divided over time of pregnancy.

The most likely estimate is based on data collected by Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (the French Agency for Food, Environmental and Occupational Health & Safety; ANSES), that estimated that, in France, 47 fetal losses due to toxoplasmosis occur annually among 2676 seroconverting pregnancies (1.7%) [21]. The high estimate is based on 75 fetal deaths in 1863 seroconverting pregnant women from four studies (1506 in Binquet et al. [22]; 144 in Foulon et al. [23]; 194 in Gras et al. [24]; 19 in Gratzl et al. [25] due to spontaneous abortions, intrauterine death, stillbirths and induced terminations and may also include fetal losses due to other causes, therefore considered to be the maximum estimate). The minimum estimate was based on a nation wide network and registry of histological and cytopathological findings in The Netherlands, where on average, an annual 0.13 diagnoses of toxoplasmosis were recorded per 100 excerpts from intrauterine fetal deaths (as cited in Havelaar et al. [18]).

The estimates from Havelaar et al. [18] are based on studies in different countries with different screening methods and include terminations of pregnancies, for which the decision making can vary between countries and their subsequent screening methods. Since data on toxoplasmosis related fetal losses are lacking in Belgium, we decided not to include fetal loss in our baseline model, but only assessed its impact in the scenario analysis.

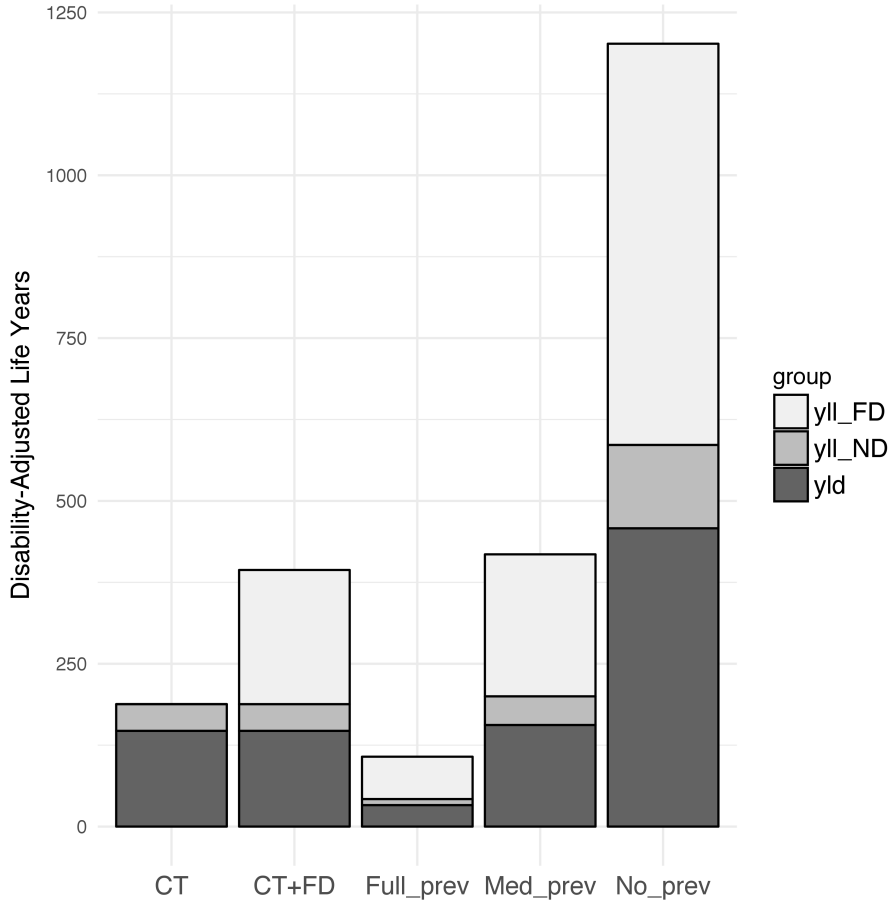
Inclusion of fetal loss resulted in an estimated 2.4 children (UI: 1.1–4.0) that died in the perinatal period and a burden estimate of 394 DALYs (UI: 188–657) in Belgium, consisting of 147 YLDs (UI: 32–344) and 247 YLL (UI: 124–392). Inclusion of fetal loss thus increased

the impact by 206 YLL (UI: 93-342). We also included the impact of fetal death in the following scenarios.

(3) CT comprehensive prevention (Full_prev): a scenario based on the seroconversion rate published in a study, in which women received comprehensive information about primary prevention. In this study by Breugelmans et al. [3] (1991–2001; supplementary Table 2), the comprehensive prevention campaign consisted of a leaflet explaining a) toxoplasmosis as a disease and b) what measures should be taken to avoid toxoplasmosis during pregnancy and these recommendations were reiterated around mid-gestation. Based on this information, we estimated an annual incidence of 15 children (UI: 6.2–29) born with CT and 0.8 children (UI: 0.6–1.0) that died in the perinatal period. The public health impact was 108 DALYs (UI: 73–159), consisting of 33 YLDs (UI: 11–73) and 75 YLL (UI: 55–97).

(4) CT medium prevention (Med_prev): in which we used a study where seronegative pregnant women received a written list of recommendations on primary prevention (1983–1990; Foulon et al. [4]; supplementary Table 2). Based on this information, we estimated an annual incidence of 73 children (UI: 40–117) born with CT and 2.5 children (UI: 1.1–4.2) that died in the perinatal period. The public health impact was 418 DALYs (UI: 240–639), consisting of 156 YLDs (UI: 63–309) and 262 YLL (UI: 134–412).

(5) CT no prevention (No_prev): a scenario based on the seroconversion rate published in a study, in which seronegative women received no information about primary prevention of toxoplasmosis (1979–1982; Foulon et al. [5]; supplementary table 2). Based on this information, we estimated an annual incidence of 213 children (UI: 119–341) born with CT and 7.2 (2.3-13) children that died in the perinatal period. The public health impact was 1203 DALYs (UI: 641–1868), consisting of 458 YLD (UI: 187–897) and 745 YLL (UI: 314–1222).



Supplementary Fig 1. Bar plot of the results of 5 scenarios examining the public health impact of congenital toxoplasmosis.

Abbreviations: CT, the scenario explained in this study; CT+FD, the scenario accounting for fetal loss ≥ 22 weeks gestation; (Full_prev): a scenario based on the seroconversion rate published in a study, in which a comprehensive prevention campaign was conducted [3]; Med_prev: in which we used a study where seronegative pregnant women received a written list of recommendations on primary prevention [4]; No_prev: a scenario in which women received no information about primary prevention [5]. We also included the impact of fetal death in the latter three scenarios; yld, years lived with disability; yll_ND, years of life lost due to neonatal death; yll_FD, years of life lost due to fetal loss.

Appendix 3 Congenital cytomegalovirus infection

Seroprevalence

Supplementary Table 5 shows the estimated summary measures and data elicited from studies published in the period 1995-2015 concerning the seroprevalence of cytomegalovirus (CMV) infection in women of childbearing age in Belgium.

Supplementary Table 5. Studies concerning the seroprevalence of cytomegalovirus infection in women of childbearing age in Belgium in the period 1995-2015

Reference	Study population	Seroprevalence % (95% CI)	n	pos	Mean Age ± SD (range)	Median Parity	Timeframe	Region/Hospital
Leuridan et al., 2012 [27]	Pregnant women	30.2 (24-37)	212	64	29.8 (22.2-39.9)	0	2006 - 2008	University of Antwerp
Francisse et al., 2009 [28]	Women in the fertility clinic	53.8 (52-56)	3227	1736	33 ± 5.6 (among seropositives)	N/A	1990 - 2006	ULB Erasme
Naessens et al., 2005 [29]	Women at prenatal consultation	56.6 (56-58)	7140	4042	29.3 (median)	1.8	1996 - 2003	UZ Brussel
Liesnard et al., 1998 [30]	Candidates for insemination	51.6 (43-61)	126	65	32.2	N/A	N/A	ULB Erasme
Cited in Kiss et al., 2002 [31][a]	Women at first gynaecological consult	32.2 (28-37)	422	136	N/A	N/A	N/A	Laboratory in the Lokeren region
Donders 1997 [32]	Pregnant women	28.3 (26-31)	1043	295	N/A	N/A	N/A	Leuven
De Schryver et al., 1997 [33]	General female population	35.8 (30-42)	229	82	(25-39)	N/A	N/A	N/A

Abbreviations: CI, confidence interval; n, sample size; pos, number of seropositive women; SD, standard deviation; UZ Brussels, University Hospital Brussels; ULB Erasme, Université Libre de Bruxelles. [u] Seroprevalence data obtained and described by Kiss et al. from a laboratory near Lokeren, East Flanders [31].

Incidence

Supplementary Table 6 shows the estimated summary measures and data elicited from studies published in the period 1995-2015 concerning the incidence of congenital cytomegalovirus (cCMV) infection in newborns in Belgium.

Supplementary Table 6. Studies concerning congenital cytomegalovirus cases in Belgium in the period 1995-2015

Reference	Study population	Incidence % (95% CI)	n	cCMV	Detection method	Timeframe	Region/city/hospital
Foulon et al., 2008 [34]	77% of all births at the UZ Brussels	0.52 (0.41-0.65)	15235	79	urine culture	1996 - 2007	UZ Brussel

Abbreviations: UZ Brussels, University Hospital Brussels; CI, confidence interval; n, sample size; cCMV, number of congenital cytomegalovirus cases.

Clinical impact

Supplementary Table 7 and 8 show the estimated summary measures and data elicited from studies concerning the percentage cCMV cases that are symptomatic at birth and cCMV related sequelae, respectively.

Supplementary Table 7. Studies concerning congenital cytomegalovirus cases symptomatic at birth (adapted from Dollard et al., [35])

Reference	n	cCMV	Number symptomatic	Symptomatic % (95% CI)	> 50% Low SES	Location, time period
Ahlfors et al.,1999 [36]	16474	76	14	18.4 (11-29)		Sweden, 1977–1986
Andersen et al., 1979 [37]	3060	12	3	25.0 (5.5-57)		Denmark, 1974–1977
Barbi et al., 1998 [38]	1268	6	0	0 (0-46)		Italy, 1994–1995
Boppana et al., 1999 [39]	20885	246	47	19.1 (14-25)	x	Alabama, 1991–1997
Casteels et al., 1999 [40]	3075	15	3	20.0 (4.3-48)		Belgium, 1996–1998
Fowler et al., 1993 [41]	17163	215	16	7.4 (4.3-12)	x	Alabama, 1980–1990
Griffiths et al., 1991 [42]	2737	9	1	11.1 (0.3-48)		London, 1983–1985
Kamada et al., 1983 [43]	2070	11	0	0 (0-29)		Japan, 1980
Melish and Hanshaw 1973 [44]	1963	20	2	10.0 (1.2-32)	x	New York, 1968–1970
Montgomery et al., 1980 [45]	954	9	2	22.2 (2.8-60)	x	Texas, 1972–1975
Numazaki and Fujikawa 2004 [46]	11938	37	5	13.5 (4.5-29)		Japan, 1977–2002
Peckham et al., 1983 [47]	14200	42	2	4.8 (0.6-16)		London, 1979–1982
Saigal et al., 1982 [48]	15212	64	4	6.3 (1.7-15)		Canada, 1973–1976
Starr et al., 1970 [49]	2147	26	2	7.7 (1.0-25)	x	Ohio, 1968
Yow et al., 1988 [50]	4840	22	2	9.1 (1.1-29)		Texas, 1981–1986

Abbreviations: n, sample size of newborns tested for cCMV; cCMV, number of congenital cytomegalovirus cases; CI, confidence interval; SES, social economic status.

Supplementary Table 8. Studies concerning congenital cytomegalovirus related sequelae (adapted from Dollard et al. [35])

Reference	Location, time period	Follow-up (years range)	n	S	A	SNHL		CD		MD		HLCD		HLMD		CDMD		ND	
						S	A	S	A	S	A	S	A	S	A	S	A	S	A
Ahlfors et al., 1999 [36]	Sweden, 1977–1986	4–7	60	11	49	1	2	1	5	0	0	2	0	0	0	0	1	0	0
Andersen et al., 1979 [37]	Denmark, 1974–1977	2	12	0	12	0	0	0	1	0	0	0	0	0	0	0	1	0	0
Barbi et al., 1998 [38]	Italy, 1994–1995	2	5	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Casteels et al., 1999 [40]	Belgium, 1996–1998	1	12	0	12	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Kumar et al., 1984 [51]	Ohio, 1968–1974	4.5–10	17	0	17	0	4	0	0	0	0	0	0	0	0	0	0	0	0
Melish and Hanshaw 1973 [44]	New York, 1968–1970	1.5–3	19	2	17	0	0	1	0	0	0	0	0	1	0	0	0	0	0
Numazaki and Fujikawa 2004 [46]	Japan, 1977–2002	7	21	0	21	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Preece et al., 1984 [52]	London, 1980–1983	0.5–3	50	3	47	1	3	0	0	0	0	0	1	2	0	2	0	0	0
Saigal et al., 1982 [38]	Canada, 1973–1976	3–5	47	3	44	1	6	1	0	0	0	0	0	0	0	0	0	0	1

Abbreviations: n, sample size; S, number of congenital cytomegalovirus cases that were symptomatic at birth; A, number of congenital cytomegalovirus cases that were asymptomatic at birth; SNHL, sensorineural hearing loss; CD, cognitive deficit; MD, motor deficit; HLCD, sensorineural hearing loss and cognitive deficit; HLMD, sensorineural hearing loss and motor deficit; ND, neonatal death.

Onset of sequelae

Supplementary Table 9 shows the estimated summary measures and data elicited from studies concerning the onset of cCMV related hearing loss. These two studies were selected based on the following criteria: hearing evaluation in the first month; a minimum of 3 hearing evaluations in the first year; at least annual follow up thereafter; and at least an average follow-up of 5 years.

Supplementary Table 9. Studies concerning the onset of congenital cytomegalovirus related hearing loss

Reference	Study period	Range no of hearing evaluations	Follow-up (months) ± SD (range)	Age of detection of hearing loss (months)	No of symptomatic children with hearing loss	No of asymptomatic children with hearing loss	Comments
Royackers et al., 2013 [53]	2003-2009	2-11	Mean 65 ± 23	1	17	11	Hearing evaluations at 1,3,(6),9,12,18,24,36,48,62,74 months
				3.7	1	0	
				4.8	1	0	Eight symptomatic children were treated with ganciclovir
				32.9	0	1	
Dahle et al., 2000 [54]	1973-1999 (?)	1-26	Median 62 (1-288)	1	37	12	Hearing evaluations at 1,3,6,9,12,18,24,30,36,48,62,..180 months
				3	10	3	
				6	10	6	
				24	13	2	
				36	5	6	
				48	1	6	
				72	5	7	
				180	4	6	

SD, standard deviation

Parameters

Supplementary Table 10 shows the parameters used to estimate the burden of cCMV in Belgium in 2013.

Supplementary Table 10. Parameters used to estimate the burden of congenital cytomegalovirus infection

Description	Value/Distribution/Method	Mean (95% UI)	Ref
Total population in Belgium in 2013	11178436		[16]
Number of live births in 2013	125606		[16]
Number of iterations	1000000		
Seroprevalence of CMV in women of childbearing age	bREM	41% (28–55)	[27-33]
Incidence of cCMV in 2013	Beta(79, 15156) * no of live births	651 infants (516–802)	[34]
Incidence of symptomatic cCMV cases	bREM	11% (6.5–16)	[35-50]
Incidence of symptomatic cCMV cases with sequelae	bREM	73% (31–99)	[35-50]
Incidence of asymptomatic cCMV cases with sequelae	bREM	12% (5.4–20)	[35-50]
Random effect meta analysis of clinical impact of cCMV	bREM	See Table 2 manuscript	[35-38,40, 44, 46,48, 51,52]
Median onset of sensorineural hearing loss in symptomatic cCMV cases (OHLS)	Gamma(1.9, 1.9)	1.0 months (0.1–2.9)	[53,54]
Median onset of sensorineural hearing loss in asymptomatic cCMV cases (OHLA)	Gamma(0.34, 0.06)	6.0 months (UI: 0–36)	[53,54]
Duration of sensorineural hearing loss in symptomatic cCMV cases	rle(OHLS/12)	80.19 years (80.08-80.24)	
Duration of sensorineural hearing loss in asymptomatic cCMV cases	rle(OHLA/12)	79.85 years (77.58-80.25)	
DW sensorineural hearing loss (DW_SNHL)	PERT(min=0.004, mode=mean(c(0.158,0.204)), max=0.307)	0.173 (0.061-0.274)	[20]
DW cognitive deficit (DW_CD)	Uniform(0.026, 0.283)	0.155 (0.032-0.277)	[20]
DW motor deficit (DW_MD)	Uniform(0.005, 0.545)	0.275 (0.019-0.532)	[20]
DW sensorineural hearing loss and cognitive deficit	1- ((1-DW_SNHL)* (1-DW_CD))	0.301 (0.144-0.439)	[20]
DW sensorineural hearing loss and motor deficit	1- ((1-DW_SNHL)* (1-DW_MD))	0.400 (0.150-0.624)	[20]
DW cognitive deficit and motor deficit	Uniform(0.018, 0.702)	0.360 (0.035-0.685)	[20]
DW neonatal or fetal mortality	1	1	[20]
Proportion symptomatic cCMV cases with chorioretinitis	Beta(7.7, 116.5)	6.2% (2.7-0.11)	[55]
Proportion asymptomatic cCMV cases with chorioretinitis	Beta(1.1, 55.8)	1.9% (0.06-6.7)	[55]

DW chorioretinitis	Beta(5.1, 472.3)	0.031 (0.018-0.048)	[20]
Proportion fetal mortality among cCMV cases	Beta(2, 42)	4.5% (0.6-12.3)	[29]

UI, uncertainty interval; CMV, cytomegalovirus infection; cCMV, congenital cytomegalovirus infection; DW, disability weight; bREM, Bayesian random effect meta-analysis using a binomial likelihood [26]; rle, residual life expectancy at age of onset according to SPMA [17]

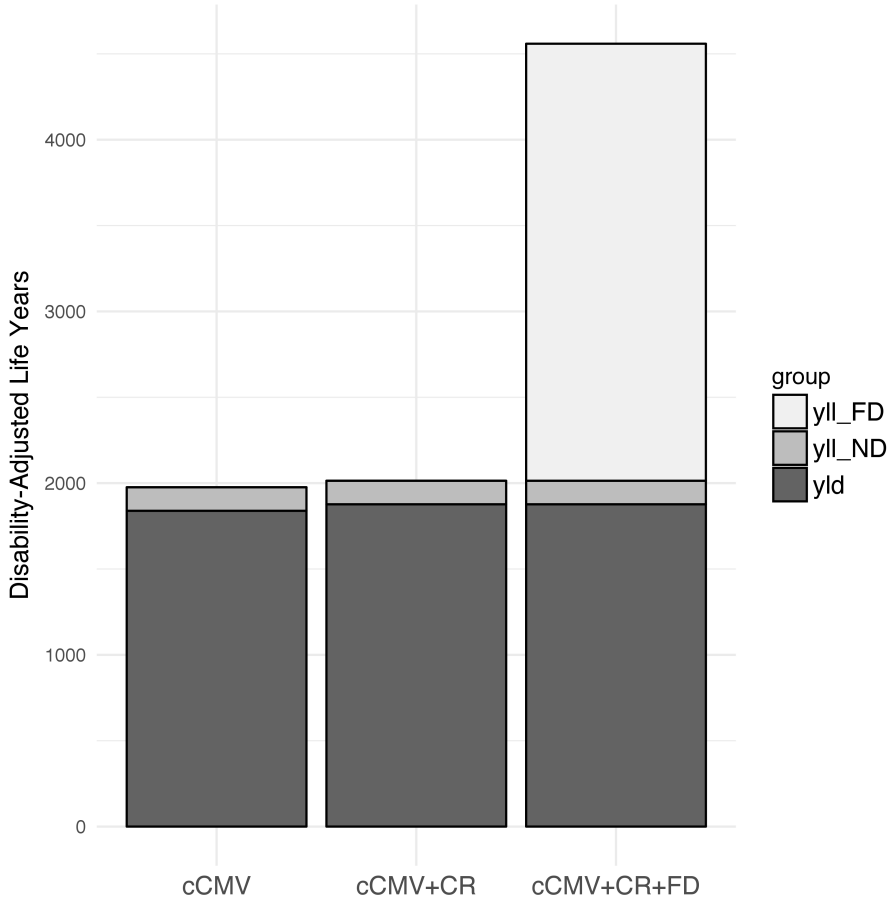
Scenario analyses

We explored the impact of the inclusion of fetal loss and visual impairment (Supplementary Fig. 2):

(1) Scenario 1 (cCMV) consisted of the results described in the manuscript. The total public health impact was 1976 DALYs (UI: 757–4067) in Belgium in 2013, which consisted of 1839 YLDs (UI: 671–3886) and 137 YLLs (UI: 0–654).

(2) Scenario 2 (cCMV+CR) explored the impact of including data on chorioretinitis. For the assessment of the extra YLD due to chorioretinitis we used information from Fowler et al. [55] and made the assumption that the incidence of chorioretinitis is the same for asymptomatic children as for children born to women with a recurrent infection. Including chorioretinitis caused an increase of 38 YLD (UI: 7.6–116) and an estimated annual public health impact of 2014 DALYs (UI: 791–4109), which consist of 1877 YLD (UI: 705–3927) and 137 YLL (UI: 0–654).

(3) Scenario 3 (cCMV+CR+FD) included both chorioretinitis and fetal loss. For the assessment of the impact of fetal loss we used information from the cohort in Brussels University Hospital from the study of Naessens et al. [29], which covers the period 1996-2003. During this period 5599 newborns were tested and 44 were found positive for cCMV of which two second-trimester abortions, with a positive CMV culture of the amniotic fluid. In this scenario we estimated an annual incidence in Belgium of 681 cCMV-infected fetuses (UI: 536–846), including 651 (UI: 516–802) live born infants and 30 (UI: 3.6– 82) fetal losses, and a public health impact of 4559 DALYs (UI: 1719–9424), which consist of 1877 YLD (UI: 705–3927) and 2682 YLL (UI: 407–7175). The extra number of YLL due to fetal loss consisted of 2545 YLL (UI: 313–7011).



Supplementary Fig 2. Bar plot of the results of 3 scenarios examining the public health impact of congenital cytomegalovirus infection.

Abbreviations: cCMV: the scenario explained in the manuscript; cCMV+CR: the scenario including chorioretinitis; cCMV+FD+CR: the scenario including chorioretinitis and fetal loss; yld, years lived with disability; yll_ND, years of life lost due to neonatal death; yll_FD, years of life lost due to fetal loss.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med, **2009**; 6:e1000097.

2. Luyasu V, Robert A, Lissenko D, *et al*. A seroepidemiological study on toxoplasmosis. Acta Clin Belg, **1997**; 52(2): 68.

3. Breugelmans M, Naessens A, Foulon W. Prevention of toxoplasmosis during pregnancy - an epidemiologic survey over 22 consecutive years. J perinat, Med, **2004**; 32: 211-214.

4. Foulon W, Naessens A, Derde MP: Evaluation of the possibilities for preventing congenital toxoplasmosis. Am J Perinatol, **1994**; 11: 57.

5. Foulon W, Naessens A, Volckaert M, Lauwers S, Amy JJ. Congenital toxoplasmosis: a prospective survey in Brussels. Br J Obstet Gynaecol, **1984**; 91: 419.

6. Torgerson PR and Mastroiacovo P. The global burden of toxoplasmosis: a systematic review. Bull World Health Organ, **2013**; 91: 501–508.

7. Antsaklis A, Daskalakis G, Papantoniou N, Mentis A, Michalas S. Prenatal diagnosis of congenital toxoplasmosis. Prenat Diagn, **2002**; 22: 1107–11.

8. Bessieres MH, Berrebi A, Rolland M, et al. Neonatal screening for congenital toxoplasmosis in a cohort of 165 women infected during pregnancy and influence of in utero treatment on the results of neonatal tests. Eur J Obstet Gynecol Reprod Biol, **2001**; 94: 37–45.

9. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet, **1999**; 353: 1829–33.

10. Jenum PA, Stray-Pedersen B, Melby KK, et al. Incidence of *Toxoplasma gondii* infection in 35,940 pregnant women in Norway and pregnancy outcome for infected women. J Clin Microbiol, **1998**; 36: 2900–6.

11. Lebech M, Andersen O, Christensen NC, et al. Feasibility of neonatal screening for *Toxoplasma* infection in the absence of prenatal treatment. Danish Congenital Toxoplasmosis Study Group. Lancet, **1999**; 353: 1834–7.

12. Robert-Gangneux F, Gavinet MF, Ancelle T, Raymond J, Tourte-Schaefer C, Dupouy-Camet J. Value of prenatal diagnosis and early postnatal diagnosis of congenital toxoplasmosis: retrospective study of 110 cases. J Clin Microbiol, **1999**; 37: 2893–8.

13. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. Obstet Gynecol, **2001**; 97: 296–300.

14. Thiébaut R, Leproust S, Chêne G, Gilbert R ; SYRCOT. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. Lancet, **2007**; 369: 115–22.

15. Wallon M, Liou C, Garner P, Peyron F. Congenital toxoplasmosis: systematic review of evidence of efficacy of treatment in pregnancy. BMJ, **1999**; 318: 1511–4.

16. Wallon M, Kodjikian L, Binquet C, et al. Long-term ocular prognosis in 327 children with congenital toxoplasmosis. Pediatrics, **2004**; 113: 1567– 72.

17. SPMA , Public Health and Surveillance (2016). Scientific Institute of Public Health, Brussels, Belgium. Available at: https://spma.wiv-isp.be/. Accessed 27 Aug 2016.

18. Havelaar AH, Kemmeren JM, Kortbeek LM. Disease burden of congenital toxoplasmosis. Clin Infect Dis, **2007**; 44: 1467-74.

19. Kortbeek LM, Hofhuis A, Nijhuis CDM, Havelaar AH. Congenital toxoplasmosis and DALYs in the Netherlands. Mem Inst Oswaldo Cruz, **2009**; 104(2): 370-373.

20. Salomon JA, Haagsma JA, Davis A, *et al*. Disability weights for the Global Burden of Disease 2013 Study. Lancet Glob Health, **2015**; 3: e712-23.

21. Binquet C, Wallon M, Quantin C, et al. Prognostic factors for the longterm development of ocular lesions in 327 children with congenital toxoplasmosis. Epidemiol Infect 2003; 131:1157–68.

22. Foulon W, Villena I, Stray-Pedersen B, et al. Treatment of toxoplasmosis during pregnancy: a multicenter study of impact on fetal transmission and children's sequelae at age 1 year. Am J Obstet Gynecol, **1999**; 180: 410–5.

23. Gras L, Gilbert RE, Ades AE, Dunn DT. Effect of prenatal treatment on the risk of intracranial and ocular lesions in children with congenital toxoplasmosis. Int J Epidemiol, **2001**; 30:1309–13.

24. Gratzl R, Hayde M, Kohlhauser C, et al. Follow-up of infants with congenital toxoplasmosis detected by polymerase chain reaction analysis of amniotic fluid. Eur J Clin Microbiol Infect Dis, **1998**; 17:853–8.

25. Derouin F, Bultel C, Roze S, et al. Toxoplasmose: état des connaissanceset évaluation du risque lié a l'alimentation [in French]. Maison-Alfort, France: Agence Française de Securité Sanitaire des Aliments, **2005**; 144-146.

26. De Vleesschauwer B, Ale A, Torgerson P, *et al*. The burden of parasitic zoonoses in Nepal: A systematic review. PLoS Negl Trop Dis, **2014**; 8(1):e2634. Doi: 10.1371/journal.pntd.0002634.

27. Leuridan E, Ieven M, Hens N, Van Damme P. High susceptebility to cytomegalovirus infection of pregnant women in Flanders, Belgium. FVV in ObGyn*,* **2012**; 4(2): 76-81.

28. Francisse S, Revelard P, De Maertelaer V, Strebelle E, Englert Y, Liesnard C. Human cytomegalovirus seroprevalence and risk of seroconversion in a fertility clinic population. Obstet Gynecol*,* **2009**; 114(2): 285-291.

29. Naessens A, Casteels A, Decatte L, Foulon W. A serologic strategy for detecting neonates at risk for congenital cytomegalovirus infection. J Pediatr, **2005**; 146: 194-197.

30. Liesnard CA, Revelard P, Englert Y. Is matching between women and semen donors feasible to avoid cytomagalovirus infection in artificial insemination with donor semen? Hum Reprod, **1998**; 13(2): 25-31.

31. Kiss P, De Bacquer D, Sergooris L, De Meester M, Vanhoorne M. Cytomegalovirus Infection: An Occupational Hazard to Kindergarten Teachers Working with Children Aged 2.5–6 Years. Int J Occup Environ Health, **2002**; 8: 79-86.

32. Donders G. Surveillance of infection during pregnancy: the boundary between routine screening and symptom-driven diagnosis [dissertation]. Leuven, Belgium, 1997 (as cited in Kiss et al., 2002).

33. De Schryver A, De Bacquer D, Van Renterghem L, De Henauw S, De Backer G. Epidemiology of cytomegalovirus in Belgium. Arch Public Health, **1997**; 55(1): 59.

34. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. Hearing loss in children with congenital cytomegalovirus infection in relation to the maternal trimester in which the maternal primary infection occurred. Pediatrics, **2008**; 122(6): e1123-e1127.

35. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol, **2007**; 17: 355-63.

36. Ahlfors K, Ivarsson S-A, Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. Scand J Infect Dis, **1999**; 31: 443–457.

37. Anderson HK, Brostrom K, Brogard Hansen K, *et al*. A prospective study on the incidence and significance of congenital cytomegalovirus infection. Acta Paediatr Scand, **1979**; 68: 329–336.

38. Barbi M, Binda S, Primache V, Clerici D ; for the NEOCMV Group. Congenital cytomegalovirus in a northern Italian region. Europ J Epidemiol, **1998**; 14: 791–796.

39. Boppana SB, Fowler KB, Britt WJ, *et al*. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. Pediatrics, **1999**; 104: 55–60.

40. Casteels A, Naessens A, Gordts F, *et al*. Neonatal screening for congenital cytomegalovirus infections. J Perinat Med, **1999**; 27: 116–121.

41. Fowler KB, Stagno S, Pass RF. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980–1990. JID, **1993**; 168: 552–556.

42. Griffiths PD, Baboonian C, Rutter D, Peckham C. Congenital and maternal cytomegalovirus infections in a London population. BJOG, **1991**; 98: 135–140.

43. Kamada M, Komori A, Chiba S, Nakao T. A prospective study of congenital cytomegalovirus infection in Japan. Scand J Infect Dis, **1983**; 15: 227–232.

44. Melish ME, Hanshaw JB. Congenital cytomegalovirus infection. Am J Dis Child, **1973**; 126: 190–194.

45. Montgomery JR, Mason EO Jr, Williamson AP, *et al*. Prospective study of congenital cytomegalovirus infection. South Med J, **1980**; 73(5): 590–593.

46. Numazaki K, Fujikawa T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. BMC Infect Dis, **2004**; 4: 22.

47. Peckham CS, Coleman JC, Hurley R, *et al*. Cytomegalovirus infection in pregnancy: preliminary findings from a prospective study. Lancet, **1983**; 1(8338): 1352–1355.

48. Saigal S, Lunyk O, Bryce Lark RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. Am J Dis Child, 1982; 136: 896–901.

49. Starr JG, Bart RD Jr, Gold E. Inapparent congenital cytomegalovirus infection. N Engl J Med, **1970**; 282: 1075–1078.

50. Yow MD, Williamson DW, Leeds LJ, *et al*. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. J Obstet Gynecol, **1988**; 158: 1189–1195.

51. Kumar ML, George AN, Jacobs IB, *et al*. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. J Pediatr, **1984**; 104: 674–679.

52. Preece PM, Pearl KN, Peckham CS. Congenital cytomegalovirus infection. Arch Dis Child, **1984**; 59: 1120–1126.

53. Royackers L, Rector E, Verhaert N, Desloovere C. Long-term audiological follow-up of children with congenital cytomegalovirus. B-ENT, **2013**; 9(suppl 21): 57–64.

54. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol, **2000**;11(5): 283–290.

55. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med, **1992**; 326(10): 663-667.