Clinical Infectious Diseases

REVIEW ARTICLE

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, [2]Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, [3]Institute of Health and Society, Université catholique de Louvain, Brussels, [4]Department of Clinical Biology, Microbiology and Immunology, Ghent University Hospital, [5]School of Life Sciences, Hasselt University, Diepenbeek, [6]Laboratory of Clinical Microbiology, AZ Sint-Lucas, Ghent, [7]Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Diepenbeek, [8]Centre for Health Economics Research & Modelling Infectious Diseases, Vaccine & Infectious Disease Institute and [9]Epidemiology and Social Medicine, University of Antwerp, and [10]Department of Public Health and Surveillance, Scientific Institute of Public Health, Brussels, Belgium

Congenital toxoplasmosis (CT) and cytomegalovirus infection (cCMV) may cause significant morbidity and 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, intrauterine 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 generation of the data needed to break the vicious circle of underrecognition.

Keywords. congenital infections; data gaps; burden of disease; DALY.

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 lead to CT [4]. CMV is a herpes virus that is spread through infected body fluids such as urine and 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 [5–7].

Knowledge about the public health impact of both 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, and 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 articles. We selected studies that reported seroprevalence and/or incidence of toxoplasmosis or CMV infections 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 between 1995 and 2015; and were based on a sample size ≥30. Duplicate data were removed.

Received 16 December 2016; editorial decision 24 March 2017; accepted 21 April 2017.

Correspondence: G. S. A. Smit, Department of Virology, Parasitology and Immunology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium (suzanne.smit@ugent.be).

Clinical Infectious Diseases® 2017;00(00):1–8

DOI: 10.1093/cid/cix344

Clinical Impact

DALY calculations require a disease model, that is, 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 and 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 metaanalysis 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 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 10 years. 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 5 years in which cCMV-infected children received repeated hearing evaluations [15, 16]. All other sequelae were assumed to be lifelong. The Belgian life expectancy table for 2012 [17] was used to estimate the duration of lifelong sequelae. The standard life expectancy table from the Global Burden of Disease (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; it was 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 disability weight [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 1 (worst possible health status), were obtained from the 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 causally related health state. 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 2 studies were found, quantitative data were summarized into a single estimate through a random effects metaanalysis in a Bayesian framework using a binomial likelihood [8, 20]. If only 2 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 Appendixes 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 2.5th and 97.5th 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 using Microsoft Excel 2011, and all calculations were performed using R 3.2.3 [21].

RESULTS

Out of 454 unique citations, 12 studies were eligible for inclusion in the analysis of the seroprevalence and incidence of (congenital) toxoplasmosis and CMV infections in Belgium (Figure 1).

Congenital Toxoplasmosis

Two studies were found concerning *T. gondii* seroprevalence in pregnant women but without any specification of age. The

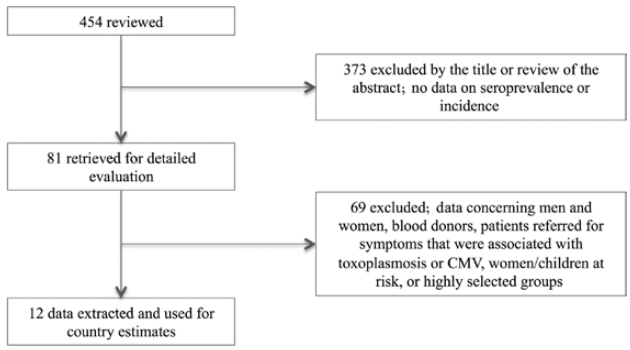

Figure 1. Flowchart showing study selection for the systematic review of recent literature on the seroprevalence and incidence of toxoplasmosis and cytomegalovirus infections in women of childbearing age and the incidence of both congenital infections in Belgium. Abbreviation: CMV, cytomegalovirus infections.

seroprevalence ranged from 49% to 50%, and the sample size ranged from 784 to 16 541 [22, 23]. A uniform distribution on this range yielded a mean seroprevalence of toxoplasmosis in pregnant women of 50% (uncertainty interval [UI], 49–50).

No reports were found concerning the incidence of congenital toxoplasmosis in Belgium. Two articles published between 1995 and 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 Luyasu et al [23] as the minimum and maximum estimates, respectively, resulted in a mean seroconversion rate of 0.22% (UI, 0.06–0.37). Our random effects metaanalysis on the data from the review by Torgerson and 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 (Figure 2).

To explore the impact of assumptions, the following scenarios on the impact of fetal death and different prevention measures (based on additional articles published before 1995; Figure 3) were analyzed: (1) CT, the scenario explained above; (2) CT including fetal death (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 3 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, 26–31]. The seroprevalence ranged from 28% to 57%, and the sample size ranged from 126 to 7140. Our random effects metaanalysis showed a seroprevalence of CMV infection in women of childbearing age of 41% (UI, 28–55).

Only 1 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 infants (UI, 516–802) were estimated to be born with cCMV infection in 2013.

Our random effects metaanalysis 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) were asymptomatic at birth. Of all infants symptomatic at birth, approximately 73% (UI, 31–99) (n = 51 [UI, 18–91])

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 (y)[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)
Central nervous system 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 years lived with disability				**147 (32–344)**	**1.3 (0.3–3.1)**
Total years of life lost				**41 (8.7–98)**	**0.37 (0.1–0.9)**
Total DALYs				**188 (43–419)**	**1.7 (0.4–3.8)**

Abbreviations: DALYs, disability adjusted life years; UI, uncertainty interval.

[a]Data adapted from Havelaar et al [10], Kortbeek et al [11], Torgerson and 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]Program Evaluation and Review Technique distribution with lower limit of profound intellectual disability (min) and upper limit of severe motor impairment (max) and the weighted mean of 1 case with severe motor impairment and 2 cases with profound intellectual disability as most likely estimate (mode).

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

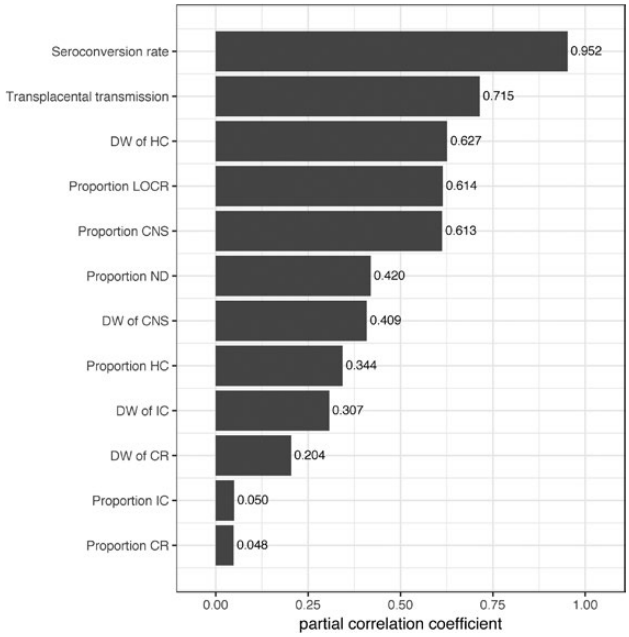

Figure 2. Variable importance analysis indicating which parameters influence the disability adjusted life years estimate for congenital toxoplasmosis in Belgium. The partial correlations coefficients show the impact of the different uncertain parameters on the uncertainty of the overall estimates. Abbreviations: CNS, central nervous system abnormalities; CR, chorioretinitis before age 1 year; DW, disability weight; HC, hydrocephalus; IC, intracranial calcifications; LOCR, late onset chorioretinitis; ND, neonatal death.

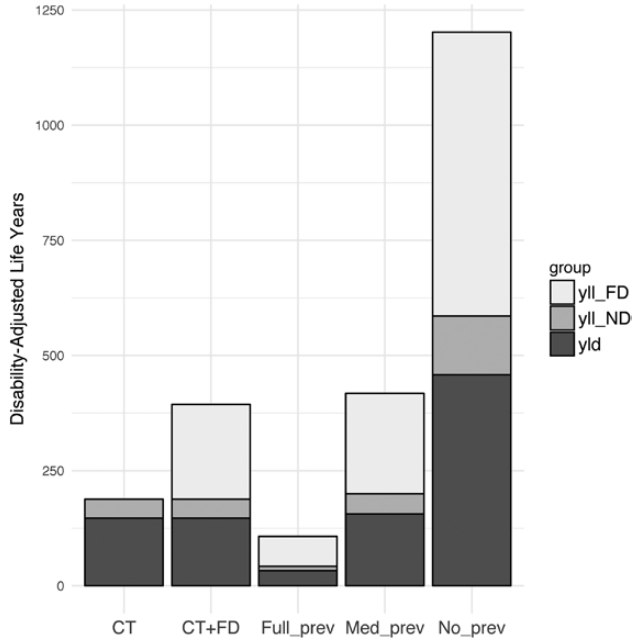

Figure 3. Bar plot of the results of 5 scenarios examining the public health impact of congenital toxoplasmosis. Abbreviations: CT: the scenario explained in this study; CT + FD: the scenario accounting for fetal loss ≥22 weeks gestation; Full_prev: a scenario based on the seroconversion rate published 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 3 scenarios); yld, years lived with disability; yll_FD, years of life lost due to fetal death; yll_ND, years of life lost due to neonatal death.

had permanent sequelae, but infants who were asymptomatic at birth developed sequelae as well (12% [UI, 5.4–20]; n = 68 [UI, 30–121]). This means that 18% (UI, 11–27) of cCMV-infected children had lifelong sequelae. The survival 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, respectively. 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; Table 2). The variable importance analysis showed that especially the uncertainty in the estimate of the proportion of children symptomatic at birth with SNHL and MD had a great impact on the DALY estimate (Figure 4).

We explored the impact of the inclusion of fetal loss and visual impairment (Figure 5). Scenario 1 (cCMV) consisted of the results explained above. Scenario 2 (cCMV + CR) explored the impact of including data on chorioretinitis, which increased the impact by 38 YLD (UI, 7.6–116) [34]. Scenario 3 (cCMV + CR + FD) included both chorioretinitis and fetal loss, in which the latter increased the impact by 2545 YLL (UI, 313–7011) [1, 34]. An overview of the data used, summary measures, and methodology is given in Supplementary Appendix 3.

DISCUSSION

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

Our analysis could not account for time-specific changes in infection rates, which may have induced an overestimation of the current incidence of both congenital infections. Since we only included studies within the reasonably short period 1995–2015, this influence may not be very large.

Only few data are available in Belgium about CT- and cCMV-related sequelae and their onset. Since cCMV-related sequelae and their onset do not seem to differ between countries, we used data available from different studies to increase the accuracy of our estimates. The CT data we used are consistent with the CT sequelae reported when predominantly type 2

Table 2. Incidence, Duration, Disability Weights, and Disease Burden of the Various Sequelae Associated With Congenital Cytomegalovirus Infection

Sequelae	Incidence Per 100 Cases[a] (95% UI)		Incidence Per Year[a] (95% UI)		Duration[b] (y)	Disability Weight[c] (95% UI)	DALYs Per Year (95% UI)	DALYs 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 + cognitive deficit	7.3 (0.02–30)	0.3 (0–1.3)	5.2 (0.01–22)	1.6 (0–7.6)	80.25	0.301 (0.144–0.439)[f]	163 (7.0–619)	1.5 (0.06–5.5)
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 years lived with disability							**1839 (671–3886)**	**17 (6–35)**
Total years of life lost							**137 (0–654)**	**1.2 (0–5.9)**
Total DALYs							**1976 (757–4067)**	**18 (6.8–36)**

Abbreviations: DALYs, disability adjusted life years; UI, uncertainty interval.

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

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

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

[d]Hearing loss: 77% of cases with hearing loss had severe to profound hearing loss [33]; therefore, we used a Program Evaluation and Review Technique (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 (DW) of comorbidity: $1–(1–DW_A)(1–DW_B)$.

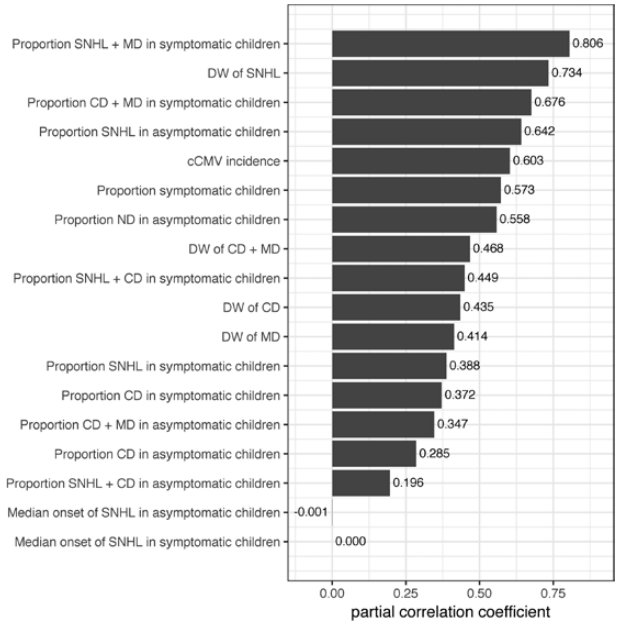

Figure 4. Variable importance analysis indicating which parameters influence the disability adjusted life years estimate for congenital cytomegalovirus infection in Belgium. The partial correlations coefficients show the impact of the different uncertain parameters on the uncertainty of the overall estimates. Abbreviations: cCMV, congenital cytomegalovirus infection; CD, cognitive deficit; DW, disability weight; MD, motor deficit; ND, neonatal death; SNHL, sensorineural hearing loss.

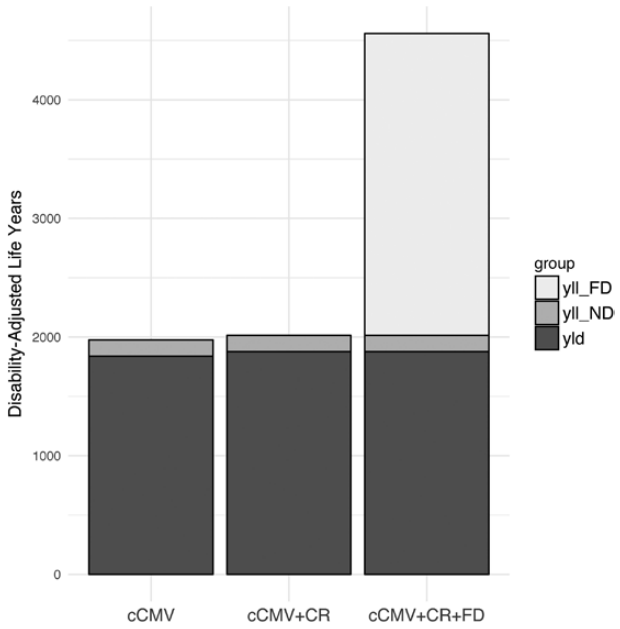

Figure 5. Bar plot of the results of 3 scenarios examining the public health impact of congenital cytomegalovirus infection. Abbreviations: cCMV: the scenario explained in this study; cCMV + CR: the scenario including chorioretinitis; cCMV + FD + CR: the scenario including chorioretinitis and fetal loss; yld, years lived with disability; yll_FD, years of life lost due to fetal death; yll_ND, years of life lost due to neonatal death.

genotypes are involved, as seen in Europe [35]. However, clinical terms used to describe sequelae in the literature and the methods used to measure sequelae were not always clearly defined or standardized across studies. Not all studies were equally thorough in ascertaining the different sequelae; standardized data on visual impairment due to cCMV and intrauterine and perinatal mortality and pregnancy termination were lacking; and the follow-up of infected children has been too short to fully identify late-onset sequelae, which might have led to underestimation of the burden [13].

We estimated a public health impact of 188 DALYs (UI, 43–419) for CT in Belgium in 2013. This is lower than the burden reported in the Netherlands (2303 DALYs, with a range of 818–6713) [11], noting that this was estimated based on an annual 194 000 live-born babies in comparison to 125 606 in Belgium and fetal loss was included in this estimate. However, our estimate was still lower when we included fetal loss (394 DALYs [UI, 188–657]). Since the same rate of occurrence and duration of sequelae were used for these estimations and the updated DWs of sequelae were not very different from earlier studies, the discrepancy is due to differences in the number of births, CT incidence estimates, and the exclusion of fetal loss in our study. Our lower CT incidence estimate (5.5 per 10 000 fetuses [UI, 1.4–10]) compared to 20 per 10 000 live births in the Netherlands [11]) can be explained by the use of data on seroconversions from 2 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* immunoglobulin (Ig) G 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 and Mastroiacovo [12] estimated a public health impact in Belgium of 230 DALYs (95% credible interval, 67–516) due to CT including fetal loss. In the European region A (EUR A; region definition of the World Health Organization) a public health impact of 2.8 DALYs per 1000 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 1000 live births. The main differences with our results relate to the CT incidence estimates and inclusion of fetal loss.

Our results provide the first estimation of the public health impact of cCMV in terms of DALYs, which was found to be higher than CT in Belgium (1976 DALYs [UI, 757–4067]). 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 been 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 unable 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 CT to a lesser extent and cCMV to a greater extent are important but currently underrecognized clinical and public health problems. De Vries et al [38] estimated that cCMV is more common than several disorders included in newborn screening. A burden of 21.8 (17.2–26.8) DALYs per 100 000 population was estimated for Down syndrome in Belgium in 2015 [39], which is comparable to our cCMV burden estimate.

Because of 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 the literature alone. Studies that identify congenitally infected children through universal neonatal screening; clearly define and report all sequelae; and extend the follow-up are needed. In addition, it is recommended that information on intrauterine and neonatal mortality and pregnancy termination be included. Furthermore, a control group should be included in each study to control bias. In Belgium, it is important to estimate the true incidence of both congenital infections based on existing routine data sources in addition to the literature.

CONCLUSIONS

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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the Research Foundation—Flanders (FWO Aspirant), Brussels, Belgium. N. H. 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; the collection, analysis, and interpretation of data; and writing of the manuscript.

Potential conflicts of interest: All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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 August 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; 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 stepwise approach. Int J Public Health **2014**; 59:571–4.
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 CD, Havelaar AH. Congenital toxoplasmosis and DALYs in the Netherlands. Mem Inst Oswaldo Cruz **2009**; 104:370–3.
12. Torgerson PR, Mastroiacovo P. The global burden of congenital toxoplasmosis: a systematic review. Bull World Health Organ **2013**; 91:501–8.
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 Pediatr Otorhinolaryngol **2012**; 76:712–7.
15. Royackers L, Rector E, Verhaert N, Desloovere C. Long-term audiological follow-up of children with congenital cytomegalovirus. B-ENT **2013**; Suppl 21:57–64.
16. 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**; 11:283–90.
17. SPMA, Public Health and Surveillance. Brussels, Belgium: Scientific Institute of Public Health, **2016**. Available at: https://spma.wiv-isp.be/. Accessed 27 August 2016.
18. Murray CJ, Ezzati M, Flaxman AD, et al. GBD 2010: design, definitions, and metrics. Lancet **2012**; 380:2063–6.
19. 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.
20. Devleesschauwer B, Ale A, Torgerson P, et al. The burden of parasitic zoonoses in Nepal: a systematic review. PLoS Negl Trop Dis **2014**; 8:e2634.
21. R Core Team. R: A language and environment for statistical computing. R Vienna, Austria: Foundation for Statistical Computing, **2015**. Available at: http://www.R-project.org/. Accessed 27 August 2016.
22. Breugelmans M, Naessens A, Foulon W. Prevention of toxoplasmosis during pregnancy—an epidemiologic survey over 22 consecutive years. J Perinat Med **2004**; 32:211–4.
23. Luyasu V, Robert A, Lissenko D, et al. A seroepidemiological study on toxoplasmosis. Acta Clin Belg **1997**; 52:68.
24. Foulon W, Naessens A, Derde MP. Evaluation of the possibilities for preventing congenital toxoplasmosis. Am J Perinatol **1994**; 11:57–62.
25. Foulon W, Naessens A, Volckaert M, Lauwers S, Amy JJ. Congenital toxoplasmosis: a prospective survey in Brussels. Br J Obstet Gynaecol **1984**; 91:419–23.

26. De Schryver A, De Bacquer D, Van Renterghem L, De Henauw S, De Backer G. Epidemiology of cytomegalovirus in Belgium. Arch Public Health **1997**; 55:59.
27. 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).
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**; 114:285–91.
29. 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.
30. Leuridan E, Ieven M, Hens N, Van Damme P. High susceptibility to cytomegalovirus infection of pregnant women in Flanders, Belgium. Facts Views Vis Obgyn **2012**; 4:76–81.
31. Liesnard CA, Revelard P, Englert Y. Is matching between women and donors feasible to avoid cytomegalovirus infection in artificial insemination with donor semen? Hum Reprod **1998**; 13(suppl 2):25–31; discussion 32–4.
32. 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:e1123–7.
33. Goderis J, De Leenheer E, Smets K, Van Hoecke H, Keymeulen A, Dhooge I. Hearing loss and congenital CMV infection: a systematic review. Pediatrics **2014**; 134:972–82.
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**; 326:663–7.
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**; 186:684–9.
36. Revello MG, Tibaldi C, Masuelli G, et al; CCPE Study Group. Prevention of primary cytomegalovirus infection in pregnancy. EBioMedicine **2015**; 2:1205–10.
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(Suppl 4):S49–53.
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. GBD compare data visualization. Seattle, WA: IHME, University of Washington, **2016**. Available at: http:// vizhub.healthdata.org/gbd-compare. Accessed 24 February 2017.