Congenital toxoplasmosis in Austria: Prenatal screening for prevention is cost-saving

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Abstract

Background
Primary infection of *Toxoplasma gondii* during pregnancy can be transmitted to the unborn child and may have serious consequences, including retinochoroiditis, hydrocephaly, cerebral calcifications, encephalitis, splenomegaly, hearing loss, blindness, and death. Austria, a country with moderate seroprevalence, instituted mandatory prenatal screening for toxoplasma infection to minimize the effects of congenital transmission. This work compares the societal costs of congenital toxoplasmosis under the Austrian national prenatal screening program with the societal costs that would have occurred in a No-Screening scenario.

Methodology/Principal findings
We retrospectively investigated data from the Austrian Toxoplasmosis Register for birth cohorts from 1992 to 2008, including pediatric long-term follow-up until May 2013. We constructed a decision-analytic model to compare lifetime societal costs of prenatal screening with lifetime societal costs estimated in a No-Screening scenario. We included costs of treatment, lifetime care, accommodation of injuries, loss of life, and lost earnings that would have occurred in a No-Screening scenario and compared them with the actual costs of screening, treatment, lifetime care, accommodation, loss of life, and lost earnings. We replicated that analysis excluding loss of life and lost earnings to estimate the budgetary impact alone.

Our model calculated total lifetime costs of €103 per birth under prenatal screening as carried out in Austria, saving €323 per birth compared with No-Screening. Without screening and treatment, lifetime societal costs for all affected children would have been €35 million per year; the implementation costs of the Austrian program are less than €2 million per year. Calculating only the budgetary impact, the national program was still cost-saving by more than €15 million per year and saved €258 million in 17 years.
Conclusions/Significance

Cost savings under a national program of prenatal screening for toxoplasma infection and treatment are outstanding. Our results are of relevance for health care providers by supplying economic data based on a unique national dataset including long-term follow-up of affected infants.

Author summary

Toxoplasma gondii is a widespread parasitic disease. In the event of primary infection during pregnancy, this parasite can be transmitted from mother to unborn child. Clinical presentation of congenital toxoplasmosis varies from asymptomatic to life-threatening risk for the fetus and infant and in later life. Prevention programs and screening strategies of health care providers vary in different countries. Austria has implemented mandatory prenatal screening for toxoplasmosis for four decades. The screening is free of charge for families and costs are covered by national health care providers. Compliance with the national program is good and outcomes for infected pregnant women and their infants since 1992 are well documented. We compared lifetime costs of screening, treatment, and follow-up with costs in a No-Screening scenario in an economic decision-analytic model. Prenatal screening resulted in substantial cost savings due to reduction in congenital toxoplasmosis and consequent injuries in affected children.

Introduction

Toxoplasma gondii (T. gondii) is a protozoal parasite that infects up to 30% of humans globally, although prevalence of infection varies widely, from 10% to 80%, among world regions and within regions [1]. While the definitive host is the cat, sources of infection for humans include food, the water supply, and organ transplants as well as direct contact with cat feces in the soil and domestic litter [1–5]. Additionally and of particular concern is maternofetal transmission during pregnancy after primary infection.

Prevalence is high in South America and tropical Africa (>50%) [6], moderate in parts of western, central, and southern Europe (30% to 50%), and relatively low (10% to 30%) in northern Europe, North America, Southeast Asia, and the Sahara [7,8]. Prevention entails adequate cooking of meat and washing of fruits and vegetables as well as drinking water free of contamination with oocysts. Educational programs for prevention, however, can only reduce infection rates, not eliminate new infections, because most people, even those who are aware of the infection routes, do not know the source of their infection [3,4,6]. Most people infected postnatally have no recognized symptoms, but immune suppression due to medical conditions or treatments can lead to serious damage to the brain and eyes as a consequence of T. gondii infection. Infection with T. gondii that occurs during pregnancy can be transmitted to the unborn child and may have serious consequences, before or after birth, even in apparently asymptomatic infected newborns [9–11]. Three European countries—Austria, France, and Slovenia—have instituted mandatory prenatal screening for primary infections of T. gondii to minimize the harmful effects of infection on infants. This is the first systematic study of the cost of a European national prenatal screening program to reduce congenital toxoplasmosis (CT) and its sequelae [12].
Congenital toxoplasmosis, risk of maternofetal transmission, and clinical manifestations

Women with primary infection with *T. gondii* during pregnancy may exhibit no symptoms, but there is about a 50% risk of transmission to the fetus and the possibility of mild to profound injury to the unborn child in untreated women [1]. The risk of maternofetal transmission increases over the course of the pregnancy, from very low risk in the first trimester to nearly 100% in the final weeks of pregnancy. In the event of transmission, risk of injury to the fetus varies inversely with gestational age, with the risk of profound injury greatest in the first trimester and the possibility of mild disease or no recognized symptoms in later stages of gestation [1,6,13,14].

Consequences of CT can include retinochoroiditis, hydrocephaly, cerebral calcifications, splenomegaly, hearing loss, blindness, and death [1,6,15,16]. In countries with prenatal screening for primary infections and consequent pre- and postnatal treatment, rates of CT and severity of symptoms in infants are lower than in countries without screening programs or compared to historical data before screening was initiated [7,10,17,18]. In comparison, a recent study of children in the United States with CT who had no pre- or postnatal treatment found that 91% of the children referred had visual and/or mental impairment by age 12 [9].

The risk of CT is complicated, however, by the diversity of genotypes of *T. gondii*. Type II predominates in Europe and was thought to be the predominant genotype in North America [6,19–21]. Recent research has identified greater diversity in US wild and domestic animals than was previously thought [22–24]. Types I and III and atypical genotypes are more common in Central and South America [25–27]. These latter strains are more virulent and are associated with ocular disease even when acquired postnatally by immune-competent persons [28]. South American genotypes are also associated with more serious injuries in CT [19,20,28–30].

Prevalence and incidence in Europe and prevention programs

Prevalence of infection with *T. gondii* varies considerably in Europe, from 7% in Norway [31], 10% in the United Kingdom [32], 19% in Italy [33], 32% in Spain [34], 33% in Austria [31,35,36], and 34% in Slovenia [37], to 37 to 44% in France [7,38] (all reported since 2000). Over the past 20 years, prevalence has fallen rather dramatically in most of the high prevalence countries coincident with national education campaigns, which have perhaps led to changes in food preparation [7,31]. Systematic screening of pregnant women also plays an educational role in highlighting the importance of food safety and hygiene for the health of the unborn.

Countries with high prevalence in the past similarly had high rates of primary infection in women during pregnancy. This may seem paradoxical since the higher the prevalence among women of child-bearing age, the higher will be the proportion of women entering pregnancy who are immune. Since prevalence, however, increases with age, the majority of young women are not immune and continue to be at risk, presumably with the same food preparation habits as before.

The substantial drop in prevalence from the 1990s to the present was accompanied by a substantial drop in maternal incidence after an initial rise [7,17]. Austria in 1974, France in 1992, and Slovenia in 1995 initiated mandatory prenatal screening programs aimed at reducing maternofetal transmission as well as the severity of injury from CT. Numerous studies have reported that systematic prenatal screening and treatment were coincident with substantial reductions in maternofetal transmission and sequelae of CT [7,10,12,13,17,18,36,37,39–45].
No systematic economic evaluation of those programs, however, has been published. The countries with systematic prenatal screening and treatment programs face the paradox of successful prevention. Now there are so few children with serious, disabling symptoms of CT that it can appear that the risk of maternal infection does not warrant the expenditure for universal prenatal screening programs. Health budgets are under continual scrutiny. In some countries political currents have changed and the assumption of state responsibility for health is questioned. Moreover, there are diverse stakeholders in the decision to allocate funds to prenatal screening or to other national health needs: the Ministry of Health, insurance funds, the Ministry of Education, social security administrations, and families of affected children.

The purpose of the current work is to compare the societal costs of CT under the Austrian national program of prenatal screening for primary toxoplasmosis with the societal costs that would have occurred in the absence of the screening program.

The Austrian national program of prenatal screening

In 1961, Thalhammer revealed a rate of CT of 78 per 10,000 live births for the Austrian population [46]. In response, mandatory prenatal screening for toxoplasma infection for all pregnant women was implemented in 1974 under the auspices of the national health care system [46,47]. This prenatal screening is part of a national prevention program called “Mother-Child-Booklet-Program” for all pregnant women and their infants through early childhood. The costs are covered by the government and the local health insurance funds; the program is free of charge for families.

The Austrian national program is described in detail in previous works [12,31,48]. Serological prenatal screening is performed ideally on a bimonthly schedule, at 8, 16, 24, and 32 weeks of gestation as well as a maternal or neonatal test for women seronegative up to the time of birth and women who have not been tested during pregnancy. In women with proven seropositivity before the current pregnancy, no further toxoplasma testing is necessary. Women who are tested and found to have been seropositive before conception require only one test. Those with suspected primary infection during pregnancy are tested twice. In Austria during this screening program, the local laboratories used 9 different test methods for the detection of IgM Toxo antibodies, each performed according to manufacturer recommendations. In the case of primary infection in a pregnant woman or to clarify suspicious test results, blood samples were retested in the reference laboratory. The Toxoplasmosis Laboratory at the Medical University of Vienna routinely uses the in-house Sabin Feldman dye test, immunosorbent agglutination assay (ISAGA)-IgM (bioMérieux, France), VIDAS Toxo IgG Avidity (bioMérieux, Frankreich), and PCR diagnostics for the detection of toxoplasma infections in pregnant women and their children.

In women with primary infection, amniocentesis and polymerase chain reaction of the amniotic fluid is recommended, but costs for those additional tests are not covered by the program. A positive result from amniocentesis identifies an affected fetus prenatally and influences the treatment during pregnancy. The routine PCR analysis used for the B1 gene after amniocentesis showed a sensitivity and specificity of 87.2% and 99.7%. Furthermore, the results revealed a positive predictive value and negative predictive value of 94.4% and 99.3% [48]. More recently, using the 529-bp PCR protocol improved sensitivity up to 100.0% [49].

Pregnant women are treated after the diagnosis of primary infection until birth, and infants with proven or suspected congenital infection are treated during the first year of life. In cases of CT, additional investigation, including cranial ultrasound, funduscopy, and complete blood count, is part of the program. The screening program reached 93% of pregnant women over
the period covered by this analysis, although the ideal schedule was not achieved for most women [31].

The Austrian Toxoplasmosis Register

The Austrian Toxoplasmosis Register records the serology history and birth outcomes for 1,387,680 pregnant women from 1992 to 2008 [12]. All cases of CT are recorded in the Register and thus it provides the basis for evaluating the costs of the program and pediatric outcomes over the 17-year period. In 10% of women no toxoplasma testing was necessary due to proven seropositivity before pregnancy. Screening confirmed additional infected women, resulting in seroprevalence of 34.4% used in the model [31]. The Register reported 70 women with primary infection of T. gondii and 8 cases of CT per year. The management of women and infants was stable, as was the rate of toxoplasma infection, during the observation period. Pediatric long-term follow-up revealed that 81% of infants with T. gondii infection did not show any clinical signs as of May 2013. All clinical variables for infection, transmission, and outcomes in infants are shown in Table 1.

Method

We retrospectively analyze data from the Austrian Toxoplasmosis Register for birth cohorts from 1992 to 2008 and clinical data from pediatric long-term follow-up to May 2013 [12]. Data were recorded at the Medical University of Vienna, Austria, in coordination with local nurses, physicians, specialists, and medical care centers. Average annual number of births was 81,628 over the 17-year period [12] and 76,547 over the last decade (www.statistik.at). We compared societal costs of illness over the lifetimes of affected children of the Austrian national program as it was carried out with the lifetime societal costs estimated in the hypothetical scenario of Austria if it had not implemented prenatal screening in those years.

We use TreeAge Pro Suite 2015 software (TreeAge Software, Inc., Williamstown, MA, USA) to construct a decision-analytic model. Using a societal perspective, we include the costs of treatment, care, and accommodation of injuries projected over the lifetimes of affected children, and lost productivity that would have occurred in a No-Screening scenario with the actual costs of screening, treatment, projected lifetime care and accommodation, and lost productivity in Austria for all of the children in the Register from 1992 to 2013.

The current work follows a template established in a decision-analytic model for a hypothetical prenatal serologic screening program for the United States [51]. The current work is the first to use clinical data on specific child outcomes with local costs to calculate the lifetime costs and benefits of a mandatory national prenatal screening program as it has been carried out over time compared to the costs that would have occurred if there had been no screening program.

The model (decision tree) contains two kinds of variables: probabilities at chance nodes (circles) and costs of outcomes at terminal nodes (triangles). Clinical variables are listed in Table 1 and represent the chance of primary infection during pregnancy, fetal infection, and pediatric clinical long-term outcomes. For the No-Screening branch, probabilities are based on international experience reported in peer-reviewed literature and synthesized in the US model [51]. Because this is a retrospective study dating back to 1992, the use of historical data for the counterfactual No-Screening scenario is appropriate. The risk of fetal infection in the No-Screening scenario is taken from the actual rate of transmission among untreated women recorded in the Austrian Toxoplasmosis Register [12]. In the Screening branch, probabilities for results at the 8-week screening are also derived from the literature in [51] because the small number of cases in the Austrian Register makes a comparison unreliable. For all other
### Table 1. Probabilities.

| Node | Test date | Clinical variable | Point estimate | References |
|------|-----------|-------------------|----------------|------------|
| 1    | No Screening decision |                  |                |            |
| 2    | Prob primary infection in pregnancy | 0.000845 | [12]          |
| 3    | Prob fetal infection | 0.508 | [12]          |
| 4    | Prob fetal death due to CT | 0.05 | [50,51]       |
| 5    | Prob asymptomatic CT | 0.06 | [1]          |
| 7    | Prob visual impairment in CT | 0.48 | [1,52]       |
| 5    | Of which mild (severe) | 0.09 (0.91) | [1,52]       |
| 5    | Prob visual and cognitive impairment in CT | 0.45 | [1,52,53] |
| 7    | Of which mild (severe) | 0.39 (0.61) | [1,52,53] |
| 5    | Prob visual, cognitive, hearing impairment, CT | 0.01 | [1,52,53] |
| 1    | Screening decision |      |                |            |
| 18   | 8 Weeks | Prob IgG(+) (maternal seroprevalence) | 0.344 | [31] |
| 19   |      | Prob IgG(+) IgM(+) | 0.000845 | [12] |
| 20   |      | Prob CT (materno-fetal transmission) | 0.034 | [1,52–54] |
| 21   |      | Prob asymptomatic CT | 0.58 | [11,13,39,43–45,55–57] |
| 21   |      | Prob visual impairment in CT | 0.3 | [11,13,39,43–45,55–57] |
| 21   |      | Prob visual and cognitive impairment in CT | 0.095 | [11,13,39,43–45,55–57] |
| 21   |      | Prob visual, cognitive, hearing impairment, CT | 0.005 | [11,13,39,43–45,55–57] |
| 21   |      | Prob fetal death due to CT | 0.02 | [50] |
| 29   | 16 Weeks | Prob IgG(+) (primary infection in pregnancy) | 0.000845 | [12] |
| 30   |      | Prob CT (materno-fetal transmission) | 0.17 [36 of 217] | [12] |
| 31   |      | Prob asymptomatic CT | 0.61 [22 of 36] | [12] |
| 31   |      | Prob visual impairment in CT | 0 | [12] |
| 34   |      | Of which requiring special school | 0.5 [5 of 10] | [12] |
| 31   |      | Prob visual, cognitive, hearing impairment, CT | 0 | [12] |
| 40   | 24 Weeks | Prob IgG(+) (primary infection in pregnancy) | 0.000845 | [12] |
| 41   |      | Prob CT (materno-fetal transmission) | 0.09 [36 of 398] | [12] |
| 42   |      | Prob asymptomatic CT | 0.86 | [12] |
| 42   |      | Prob visual impairment CT (1 w/ hearing loss) | 0.056 [2 of 36] | [12] |
| 42   |      | Prob visual and cognitive impairment in CT | 0.056 [2 of 36] | [12] |
| 45   |      | Of which cerebral toxoplasmosis | 0.5 [1 of 2] | [12] |
| 45   |      | Of which physical impairment | 0.5 [1 of 2] | [12] |
| 42   |      | Prob visual, cognitive, hearing impairment, CT | 0 | [12] |
| 51   | 32 Weeks | Prob IgG(+) (primary infection in pregnancy) | 0.000845 | [12] |
| 52   |      | Prob CT (materno-fetal transmission) | 0.13 [48 of 368] | [12] |
| 53   |      | Prob asymptomatic CT | 0.79 [38 of 48] | [12] |
| 53   |      | Prob visual impairment in CT | 0.13 [6 of 48] | [12] |
| 53   |      | Prob visual or cognitive impairment in CT | 0.08 [4 of 48] | [12] |
| 56   |      | Of which cerebral toxoplasmosis | 0.75 [3 of 4] | [12] |
| 57   |      | Of which requiring special school | 0.33 [1 of 3] | [12] |
| 56   |      | Of which physical impairment | 0.25 [1 of 4] | [12] |
| 53   |      | Prob visual, cognitive, hearing impairment, CT | 0 | [12] |
| 63   |      | Prob no PCR of amniotic fluid | 0.43 | [12] |
| 66   | 40 Weeks | Prob IgG(+) (primary infection in pregnancy) | 0.000845 | [12] |

(Continued)
branches of the Screening arm, the probabilities are calculated from the Austrian Toxoplasmosis Register and thus represent actual Austrian experience recorded by the Toxoplasmosis Laboratory at the Medical University of Vienna, Vienna, Austria [12].

Costs of serology, treatment, and lifetime costs of special care and lost productivity for affected infants and their parents are listed in Table 2. Costs of serology, other tests, and medications are derived from recorded expenses of the Austrian program from the years 1999–2013 and adjusted to 2012 prices. For test and medication costs we use the average of costs reported by health insurance funds. Lifetime costs of injuries of CT include treatment, accommodation, special schooling, loss of earnings for affected infants, and loss of parental earnings. Earnings are used as a proxy for the lifetime productivity that is lost by the family and the society for infants affected by CT and their parents. Estimates of costs are derived from the literature for Austria (adjusted to costs for 2012) and, when necessary, for neighboring countries (adjusted to Austrian costs for 2012). Direct costs and productivity losses are discounted annually at 3% for as long into the future as each cost occurs. Direct costs for medication represent average maternal and infant treatment costs. Costs of special treatment are assigned to the actual child outcomes in the Austrian Register [12]. Detailed explanation of cost derivation can be found in the methodological supplement, S1 Methods. For the cost assigned to death, in utero or neonatal, we derive a Value of Statistical Life (VSL) for Austria in 2012 using the recommendation of the OECD (Organization of European Cooperation and Development), which is based on a meta-analysis of more than 800 studies of VSL [58]. The background on the use of VSL and the derivation of our estimate for Austria are explained in the methodological supplement, S1 Methods.

In addition to the costs that are assigned to each outcome as terminal nodes in the tree, we include the costs of amniocentesis with PCR, which is assigned to the group of women with primary infection. It is unnecessary to assign the costs to specific women because it does not change the overall costs. In Austria over the period, 60% of women with gestational toxoplasmosis infection underwent amniocentesis. The cost of PCR, which was €363.45, was absorbed by the local prenatal care centers. The total cost was almost €256,000. Since the decision tree calculates the cost per birth in the country, we assign the cost of PCR as overhead on all 1,387,680 births over the period. It is expected that the cost of PCR will drop significantly in the near future, to an estimated €100 when the testing is done routinely, reducing costs overall. Although the women and their insurers did not bear the cost, the expense does represent a societal cost and so we include it in the analysis.

The decision tree shows the probabilities of all possible outcomes and the costs associated with each outcome. In Fig 1, each outcome has a conditional probability that is the product of the probabilities along each branch. The formulas at the terminal nodes for each outcome list the direct and indirect costs that are explained in Table 2.
The method outlined above is the conventional way to calculate the lower-cost option, including societal costs that are borne by affected infants, their families, and the economy as a whole, regardless of who pays. There could be times, however, that a Ministry of Health or other institution would like to know just the impact of a program on the government budget, not societal cost. For that reason, we also calculate the cost-saving option considering only those costs paid by government and public insurance funds, that is, omitting lost productivity of affected children and their parents and VSL.

Table 2. Direct and indirect costs.

| Variable name | Description | Present value in euros (2012) | Source |
|---------------|-------------|-----------------------------|--------|
| Test and medication costs | Fundus | Indirect funduscopcy cost | 54.26 a |
| | InflGtest | Infant IgG test cost | 13.48 b |
| | InflMtest | Infant IgM test cost | 17.69 b |
| | MatIgGtest | Maternal IgG test cost | 6.50 b |
| | MatIgMtest | Maternal IgM test cost | 6.89 b |
| | PedCBC | CBC during pediatric treatment | 24.85 c |
| | PedConsult | Pediatric consultation cost* | 0 a |
| | PedCranialUltra | Pediatric cranial ultrasound cost | 90.71 a |
| | PedECG | Pediatric ECG cost | 18.05 c |
| | PedRx | Pediatric treatment costs 12 months | 160.26 d |
| | RxNegPCR | Maternal treatment costs with negative PCR of amniotic fluid | 181.78 d |
| | RxPosPCR | Maternal treatment costs with positive or no PCR of amniotic fluid | 178.32 d |
| Direct costs due to impairments | Cerebral | Treatment costs for cerebral CT | 30,458 e, [59] |
| | CognMild | Treatment costs for mild cognitive impairment | 66,071 e, [59] |
| | CognSevere | Treatment costs for severe cognitive impairment | 445,536 e, [59] |
| | HearingMild | Treatment costs for mild hearing impairment | 20,924 e |
| | SpecEdBlind | Special school costs for severe visual impairment | 86,239 e, [60] |
| | SpecEdMildCogn | Special school costs for mild cognitive impairment | 73,699 e, [60] |
| | SpecEdSevereCogn | Special school costs for severe cognitive impairment | 713,141 e, [60] |
| | VisualMild | Treatment costs for mild visual impairment | 1,576 e, [60] |
| Indirect costs due to impairments | ChildPyLoss | Productivity loss for severe cognitive impairment | 561,721 e, [61,62] |
| | ParentPyLoss | Productivity loss of parents | 33,940 e, [60,63] |
| | VisualSevere | Income loss and non-medical costs of severe visual impairment (for societal costs) | 393,624 e, [64] |
| | VisualSevere | Non-medical costs of severe visual impairment (for budget impact only) | 327,594 e, [64] |
| | VSL | Value of a statistical life | 5.85 million e, [58] |
| | | Value of a statistical life (for budget impact only) | 0 |

* The standard pediatric protocol includes 5 well-baby consultations, so there is no additional expense for infants with CT.

Sources:

a. Average for all 9 regional health insurance funds: Burgenländische Gebietskrankenkasse, Kärntner Gebietskrankenkasse, Niederösterreichische Gebietskrankenkasse, Oberösterreichische Gebietskrankenkasse, Salzburger Gebietskrankenkasse, Steiermärkische Gebietskrankenkasse, Tiroler Gebietskrankenkasse, Vorarlberger Gebietskrankenkasse, Wiener Gebietskrankenkasse;

b. Average Austrian laboratory costs, numerous payers;

c. BMGF, Austrian Federal Ministry of Health;

d. Cost of treatment for health insurance funds;

e. See methodology supplement, S1 Methods.

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To test the robustness of our results to variations in costs, we perform a sensitivity analysis using an Incremental Tornado diagram varying all costs -10% and +10%, except for test costs, which have a lower bound of €4, and VSL, which is given a range of €800,000 to €6,700,000. The former amount represents only the discounted valuation of productivity loss over the lifetime, and the latter amount is the upper bound of the OECD estimate of VSL. (See S1 Methods for explanation of VSL derivation.)
Ethics statement

The maternal screening study was approved by the local ethics committee at the Medical University of Vienna, Vienna, Austria (824/2009). All adult subjects and parents of any child participants gave their informed consent orally in person or by telephone at the time of inclusion. The individuals were included in the nationwide toxoplasmosis register performed 1992–2008 and their oral consent was documented in the register data file. Written consent could not be obtained, due to the fact that this was a nationwide study. The data were processed anonymously. The current economic study utilized anonymous data from the national screening program.

Results

In Austria, a country with a moderate seroprevalence of *T. gondii* during childbearing years, we recorded a total of 1,387,680 women giving birth between 1992 and 2008 (www.statistik.at). Fig 2 shows the decision tree after calculation of the lower-cost option, based on the probability of each outcome and the costs associated with each. As shown in Fig 2, and summarized in Table 3, lifetime societal costs of CT sequelae in the No-Screening scenario would have been €426 per birth, or about €35 million for all Austrian births in one year. Total societal costs in Austria that would have occurred without prenatal screening for nearly 1.4 million births over the 17 years would have been about €591 million, including costs for lifelong treatment and accommodation, as well as loss of earnings for affected children and their parents.

In contrast, prenatal screening for toxoplasma infections according to the Austrian national program including costs of screening, maternal treatment, infant treatment, and lifetime costs for those infants with CT sequelae amounted to €103 per birth. The total cost of the Screening scenario, including lifetime costs of CT sequelae, was €8.4 million for all births in one year for Austria, or €143 million for 1.4 million births in the 17-year period.

As shown in Table 3, the prenatal screening option resulted in savings of €323 per birth, or about €26 million per year compared to No-Screening. For all births, screening saved about €448 million in 17 years.

Adding the cost of amniocentesis with PCR for 60% of the women with primary toxoplasma infection during pregnancy increased the cost per Austrian birth in the period by about €0.18, changing the difference in cost per birth of the entire screening and treatment program by a trivial amount.

Actual program costs and the cost of CT for an affected child

The TreeAge program calculates all of the costs that occur in each scenario—the counterfactual (No screening) compared to all actual lifetime costs in Austria resulting under the screening scenario. Thus the TreeAge program attributes costs to the Screening scenario that result from treating infants who are infected despite the program, including those whose mothers were not screened or were screened inadequately, with the lifetime costs of follow-up, accommodation, and parental work time lost. In Austria, if there were no screening program, one must assume that the state would provide health care for a child born with, or who later develops, CT symptoms. So the costs of diagnosing and caring for a symptomatic infected child are not really costs of the screening program itself. They would occur (and in much larger numbers) without the national screening. The €8.4 million a year under the Screening scenario represents the costs of the screening program plus the lifetime societal cost for the affected children born during the 17-year period.

The screening program itself entails very little cost. It includes only testing all pregnant women (except those already known to be seropositive) and treating women with primary
Fig 2. Decision tree after calculation. Tree showing results for societal costs.

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infection. It also would include the cost of treating the very few asymptomatic infected infants because without screening they would be missed, but with screening, they would be treated from birth. Under the screening program, there have been 70 incident infections in mothers per year. Without treatment, there would be a fetal infection rate of 0.508 [12] and a probability of asymptomatic CT of 0.06 [1]. Thus, there would be two asymptomatic infected newborns treated per year because of the screening program who would have been overlooked without screening (70 x 0.508 x 0.06 = 2.10). Costs for each of those children would be: 5 infant IgG test, 5 infant IgM test, pediatric treatment, CBC, ECG, cranial ultrasound, and 17 funduscopies, which amount to €1,372.

The costs of the screening program, shown in Table 4, total approximately €1.9 million per year for all pregnancies, or €25 per pregnancy. A new diagnostic appears likely with a test cost of about €4. Recalculating with a test cost of €4 would reduce the total cost of prenatal screening and maternal treatment from about €1.9 to about €1.2 million (calculation not shown).

The costs of the screening program can be compared to the cost of caring for a child whose mother is not treated. The costs for individual services and productivity losses are listed in Table 2, but each symptomatic child generates multiple kinds of costs. In the tree before rollback (calculation), Fig 1, all the costs for an individual child for each outcome are listed at the terminal node. For example, in the No-Screening scenario, a child with severe visual, cognitive, and hearing impairment (Terminal node #14 in Fig 1) will incur the following costs (assuming symptoms at birth that lead to testing, treatment, and follow-up care): 5 infant IgG tests, 5 infant IgM tests, pediatric treatment, CBC, ECG, cranial ultrasound, and 17 funduscopies, as well as the direct costs and productivity losses for child and parents associated with severe visual, cognitive, and hearing impairment, and special education costs.

Fig 2 (Terminal node #14) shows the sum of those costs. The lifetime cost for one child with severe visual, cognitive, and hearing impairment is €1.8 million (€1,778,210). Thus the costs of the entire screening program for one year are nearly the same as the potential costs for

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**Table 3. Results.**

| Scenario    | Societal costs (euros) | Budgetary costs (euros) |
|-------------|------------------------|-------------------------|
|             | Cost per birth | Cost for all births in one year | Costs for all births 1992–2008 | Cost per birth | Cost for all births in one year | Costs for all births 1992–2008 |
| No Screening| 426          | 34,756,486               | 590,862,267                  | 219         | 17,905,970                   | 304,401,485                  |
| Screening   | 103          | 8,422,401                | 143,180,822                  | 33          | 2,711,690                    | 46,098,730                   |
| Saving      | 323          | 26,334,085               | 447,679,445                  | 186         | 15,194,280                   | 258,302,755                  |

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**Table 4. Annual cost of the screening program.**

| Category                                                   | Number affected | Unit cost euros (2012) | Total cost euros (2012) |
|-------------------------------------------------------------|-----------------|------------------------|-------------------------|
| Average annual number of pregnancies since 2000             | 76,547          |                        |                         |
| minus 10% of women already identified IgG+                  | 7,655           |                        |                         |
| Women needing initial IgG                                   | 68,892          | 6.50                   | 447,800                 |
| Women needing IgM (assuming 34% prevalence minus 10% identified) | 18,370          | 6.89                   | 126,570                 |
| Women IgG− needing 4 more tests                            | 50,520          | 4 x 6.50               | 1,313,550               |
| Primary infections requiring treatment                      | 70              | 180                    | 12,600                  |
| Amniocentesis cost                                         | 42              | 363.45                 | 15,265                  |
| Asymptomatic CT newborns tested and treated                | 2               | 1,372                  | 2,744                   |
| Total cost of prenatal screening and treatment              |                 |                        | €1,918,529              |

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a single severely affected child whose mother was not treated. A child with only severe visual impairment generates costs of €482,811 (at terminal node #9). The costs for four such children exceed the annual cost of the screening program. Without prenatal treatment, more than 90% of infected children have been found to have some form of serious impairment [1,9,32,53]. Prenatal screening with pre- and postnatal treatment as needed prevents or mitigates most injuries.

Austria has 70 primary infections per year [12]. If we assume 50% maternofetal transmission without prenatal treatment, as seen in Austrian women who were not treated [12], that would be 35 cases of CT each year, rather than the 8 cases per year under the treatment program, with symptoms ranging from mild visual impairment to fetal death. Because the model calculates costs on a population basis, the cost of €426 in the tree is a cost per Austrian birth, which is multiplied by the number of births, resulting in potential costs of €35 million for the 35 children who would be infected under the No-Screening scenario. The screening program costs €1.9 million per year while the societal costs of the No-Screening scenario are €35 million per year.

It is useful to see these costs in relation to overall Austrian government spending and Gross Domestic Product (GDP). The annual cost of the screening and treatment program is 0.007% of total Austrian public spending on health and 0.003% of overall Austrian government spending. The annual cost of the program is 0.0006% of Austrian GDP (Derived from data at www.focus-economics.com/country-indicator/austria/gdp-eur-bn; World Development Indicators, www.wdi.worldbank.org).

Budget impact
Calculating just the impact on the Austrian public budget—that is, omitting the lifetime costs of lost earnings that fall on affected children, their families, and society, and VSL for fetal and infant deaths, we find that the maternal screening program is still cost-saving. As seen in Fig 3, and summarized in Table 3, expenditures by government and government-sponsored insurers, based on Austrian experience over the period 1992 to 2008, cost €33 per birth compared to an estimated €219 per birth if the prenatal screening program had not been implemented in Austria. (As explained above, this overstates the budgetary cost of the screening program itself because it includes diagnosis and care of children who would be cared for under the Austrian health care system even without a screening program.) Even from the extremely narrow budgetary perspective, the Austrian national program has more than paid for itself in reducing the costs to the state and state-sponsored institutions of treating and educating children injured by CT by €186 per birth for 1.4 million births over the period. That amounts to a total budgetary saving of more than €258 million, or more than €15 million per year.

Sensitivity analysis
Results of the sensitivity analysis show that the savings both to society and to the government budget are robust to variations in all costs. Varying costs by ±10% had a trivial effect on cost per birth in the No-Screening and Screening scenarios and consequently on the savings that result from screening, for both the full societal cost and for the public budget. Fig 4 shows an Incremental Tornado Analysis from the societal perspective. The x axis shows the difference in costs per birth between the No-Screening and Screening scenarios with an Expected Value (EV) of €323. The horizontal bars show the full variation in the Expected Value (savings per birth) resulting from the range of values for each cost parameter. Both Fig 4 and Table 5 demonstrate the trivial impact on the large savings that result from screening. The variation in VSL had the greatest effect on costs, but even then the difference between low and high values for
Fig 3. Decision tree for budget impact. Tree showing results, budget impact.

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savings was only €56 and the savings from screening never fell below €275 per birth. Fig 5 shows the one-way sensitivity analysis on VSL in the societal model, which again demonstrates that whether one includes only the loss of earnings (€800,000) or the upper bound of the OECD estimate for VSL (€6.7 million), there is little impact on the savings derived from the screening program, showing the same minimum savings of €275 per birth seen in Fig 4 and Table 5.

Fig 6 shows the Incremental Tornado Analysis for the Budget impact. The Expected Value, that is savings per birth, is €186. The variation in savings per birth never exceeds €17 and the minimum savings from the screening program for the budget is never less than €178 per birth, as seen also in Table 6.

Discussion

In this retrospective study we compare the costs for a national program of prenatal screening for *T. gondii* with a No-Screening scenario for Austria, a country with moderate seroprevalence
in women of childbearing-age and 1,387,680 births over the years 1992 to 2008. There have been few economic analyses of CT-prevention programs [51,65]. To our knowledge this is the first report of an economic decision-analytic model incorporating surveillance data from pregnancy through long-term pediatric follow-up for an entire nation over nearly two decades of observation. Thus our data are of special interest for physicians, health care providers, and policy makers in considering the implementation of a prevention program for CT.

The substantial reductions in primary infection, maternofetal transmission, and fetal and child injuries resulting from *T. gondii* infection during the implementation of the Austrian prenatal screening program from 1992 to 2008 have been reported elsewhere [12]. In the current work, our major finding demonstrates that a national program of prenatal screening and treatment to prevent congenital toxoplasmosis or reduce clinical symptoms in affected infants is cost-saving for governmental health care providers and for Austrian society. Under the Austrian national prenatal screening program, total societal savings are €323 per birth. Consequently, the screening program saved about €448 million in costs to Austrian society for the birth cohorts from 1992 to 2008. Even in narrowly budgetary terms, the prenatal screening program has saved the Ministry of Health, the Ministry of Education, and government-sponsored insurance funds €186 per birth, or more than €258 million over the period, averaging more than €15 million a year, because of injuries prevented in children of women with primary toxoplasma infection. Even large variations in all costs make little difference in results. This is not surprising given the profound injuries that can occur without treatment and the low cost of the intervention.

### Table 5. Incremental tornado risk report, societal perspective: Savings from screening.

| Variable                                | Variable range (euros) | Savings from screening |
|-----------------------------------------|------------------------|------------------------|
|                                         |                        | Low (euros) | High (euros) | Spread (euros) |
| Value of statistical life for fetal or infant death | 800,000 – 6,700,000 | 274.61     | 330.68      | 56.07         |
| Special school costs for severe cognitive impairment | 641,827–784,455 | 314.33     | 327.77      | 13.44         |
| Income loss and non-medical costs of severe visual impairment | 354,262–432,986 | 315.99     | 329.62      | 13.63         |
| Productivity loss for severe cognitive impairment | 505,549–617,893 | 316.09     | 329.12      | 13.03         |
| Maternal IgG test cost                  | 4–7                   | 320.80     | 331.66      | 10.86         |
| Treatment costs for severe cognitive impairment | 400,982–490,090 | 317.44     | 327.77      | 10.34         |
| Special school costs for severe visual impairment | 77,615–94,863 | 321.07     | 324.14      | 3.07          |
| Maternal IgM test cost                  | 4–8                   | 322.22     | 323.60      | 1.38          |
| Special school costs for mild cognitive impairment | 66,329–81,069 | 322.19     | 323.03      | 0.84          |
| Productivity loss of parents            | 30,546–37,334         | 322.21     | 323.00      | 0.79          |
| Treatment costs for mild cognitive impairment | 59,464–72,678 | 322.44     | 322.77      | 0.34          |
| Treatment costs for cerebral CT         | 27,412–33,504         | 322.47     | 322.74      | 0.27          |
| Infant IgM test cost                    | 4–9                   | 322.59     | 322.75      | 0.16          |
| Infant IgG test cost                    | 4–15                  | 322.59     | 322.71      | 0.12          |
| Treatment costs for mild visual impairment | 1,418–1,734         | 322.55     | 322.66      | 0.11          |
| Maternal treatment costs with no CT     | 164–200               | 322.58     | 322.63      | 0.05          |
| Indirect funduscopy cost                | 49–60                 | 322.58     | 322.63      | 0.05          |
| Pediatric cranial ultrasound cost       | 82–100                | 322.59     | 322.62      | 0.04          |
| Maternal treatment costs with CT        | 160–196               | 322.59     | 322.62      | 0.02          |
| Pediatric treatment costs 12 months     | 144–176               | 322.60     | 322.61      | 0.02          |
| Treatment costs for mild hearing impairment | 18,832–23,016       | 322.60     | 322.61      | 0.02          |
| CBC during pediatric treatment          | 22–27                 | 322.60     | 322.61      | 0.00          |
| Pediatric ECG cost                      | 16–20                 | 322.61     | 322.61      | 0.00          |

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Even in a country where prevalence is falling due to greater awareness and success of primary prevention, prenatal screening is needed. Lower prevalence means that more women enter pregnancy susceptible to infection. Since seroprevalence increases with age, women in their childbearing years are among the vulnerable population that has grown over the past decades as prevalence has declined.

Under the Austrian national program of prenatal screening, there has been a dramatic reduction in maternofetal transmission of *T. gondii* and in the degree of injury in affected children compared to historical data before implementing the prenatal screening [46,47]. Interestingly, the Austrian Toxoplasmosis Register shows even greater success in child outcomes than observed in France even though the French protocol mandates monthly testing, compared to the Austrian program of bimonthly testing [12]. It seems, however, that in Austria, while women are attending prenatal checkups, most are not receiving the recommended number of blood tests for primary toxoplasma infection [12,31,35]. Education of women and obstetric staff should be a relatively inexpensive solution that would improve even further the success of the Austrian CT-prevention program and increase the cost saving beyond what we have measured based on actual experience.

Further examination of the Austrian data demonstrates that 49% of amniocentesis testing was unnecessary and was not based on a primary infection during pregnancy [48]. Such testing is expensive and brings unnecessary risk to the unborn and anxiety to parents. Ongoing education for gynecologists should help to eliminate this unnecessary cost and risk.

In sum, while the Austrian prenatal screening protocol to minimize the effects of primary infections of *T. gondii* during pregnancy is cost-saving, additional cost saving could be achieved by enhancing the education of obstetric staff. There is a need to increase the number of susceptible women who receive the recommended number of screening blood tests at the...
recommended intervals. There is also a need to use amniocentesis only when indicated by proven primary infection during pregnancy.

Challenges facing prevention programs

Successful screening and treatment programs, such as Austria’s, face two challenges, both of which derive from their success. As with other public health programs, the European prenatal screening programs and education campaigns confront the paradox of success. People do not see or hear about infants affected by CT as they did in the past when infant deaths or profound brain injuries and visual impairment of varying degrees were more common, due to high rates of CT. Prevention programs only seem expensive in the absence of disease. In the face of budget pressure, the absence of infants with injuries of CT can be misunderstood to mean there is no longer a risk. On the contrary, it has taken two decades of successful prenatal screening and treatment to make the risk invisible. Moreover, the success of education programs in reducing prevalence in the population, while it may protect women by making them more aware of the
The second challenge to the prenatal screening programs comes from the methodological debate over the validity of observational studies versus randomized controlled trials as the evidence base for interventions. Numerous authors have suggested that the question of efficacy of prenatal screening and treatment can only be adequately answered with randomized controlled trials (RCTs) [13, 39, 66, 67]. RCTs, however, pose an insurmountable ethical problem in countries where prenatal screening has been associated with significant improvement in outcomes for infants whose mothers were treated prenatally. An RCT requires equipoise, which is lacking in countries with successful screening programs (Austria, France, and Slovenia, for example) and in countries with similar epidemiology and access to care. Without equipoise, it is doubtful that one could construct an ethical trial that would require random assignment of some pregnant women to denial of a treatment with demonstrated efficacy [6, 7]. Blinding could be incompatible with informed consent. It is also unlikely that such trials would have sufficient power because, with informed consent, few parents would be likely to choose not to medicate. The resulting selection bias would also invalidate the results of the trial. This ethical question is not unique to prenatal screening programs for CT. Interventions to reduce smoking, for example, were implemented based on observational data. Any RCT assigning participants to smoking would not have passed ethical review. It has been impossible to construct valid RCTs for treating sexually transmitted diseases to reduce HIV incidence because observational studies and an earlier trial demonstrated that such treatment is beneficial [68]. Similarly, any other effective treatments for cofactor infections cannot ethically be withheld from controls [68, 69]. Observational and historical data from Austria, France, and Slovenia, and

### Table 6. Incremental tornado risk report, budget impact: Savings from screening.

| Variable                                             | Variable range (euros) | Savings from screening |
|------------------------------------------------------|------------------------|------------------------|
|                                                      | Low (euros)            | High (euros)           | Spread (euros) |
| Special school costs for severe cognitive impairment | 641,827–784,455        | 177.86                 | 194.41         | 16.55         |
| Non-medical costs of severe visual impairment        | 294,835–360,353        | 180.30                 | 191.97         | 11.67         |
| Maternal IgG test cost                               | 4–7                   | 184.33                 | 195.19         | 10.86         |
| Treatment costs for severe cognitive impairment      | 400,982–490,090        | 180.97                 | 191.31         | 10.34         |
| Special school costs for severe visual impairment    | 77,615–94,863          | 184.60                 | 187.67         | 3.07          |
| Maternal IgM test cost                               | 4–8                   | 185.76                 | 187.13         | 1.38          |
| Special school costs for mild cognitive impairment   | 66,329–81,069          | 185.72                 | 186.56         | 0.84          |
| Treatment costs for mild cognitive impairment        | 59,464–72,678          | 185.97                 | 186.31         | 0.34          |
| Treatment costs for cerebral CT                      | 27,412–33,504          | 186.01                 | 186.27         | 0.27          |
| Infant IgM test cost                                 | 4–19                  | 186.12                 | 186.28         | 0.16          |
| Infant IgG test cost                                 | 4–15                  | 186.12                 | 186.24         | 0.12          |
| Treatment costs for mild visual impairment           | 1,418–1,734            | 186.09                 | 186.19         | 0.11          |
| Maternal treatment costs with no CT                   | 164–200               | 186.11                 | 186.17         | 0.05          |
| Indirect funduscropy cost                            | 49–60                 | 186.11                 | 186.16         | 0.05          |
| Pediatric cranial ultrasound cost                     | 82–100                | 186.12                 | 186.16         | 0.04          |
| Maternal treatment costs with CT                      | 160–196               | 186.13                 | 186.15         | 0.02          |
| Pediatric treatment costs 12 months                  | 144–176               | 186.13                 | 186.15         | 0.02          |
| Treatment costs for mild hearing impairment           | 18,832–23,016         | 186.13                 | 186.15         | 0.02          |
| CBC during pediatric treatment                        | 22–27                 | 186.14                 | 186.14         | 0.00          |
| Pediatric ECG cost                                   | 16–20                 | 186.14                 | 186.14         | 0.00          |
perhaps even comparative data from the United States, have eliminated the equipoise necessary for an ethical RCT of prenatal screening and treatment for primary infection of *T. gondii*. The European screening programs for CT have had noteworthy success, reducing the number of deaths and profound injuries in affected infants. That success itself in reducing preventable suffering and death commends the programs for continuation. The cost savings for national health care systems and society at large reinforce the argument for continuation.

CT is a health problem worldwide and it is not possible to eliminate all sources of infection for pregnant women, nor is a vaccine likely to be developed in the near future. There are, however, successful CT-prevention programs that are reducing clinical effects of CT and saving money for national health administrations and cost to society.

**Limitations**

Our results understate the benefits of following the Austrian national program because the costs associated with injuries to infants whose mothers were not tested in accordance with the protocol are attributed to the screening scenario [31]. If those mothers had been tested on schedule, the injuries in the infants would most likely have been fewer and less severe, as was the case for the infants tested on schedule. Another source of overstatement of costs of actual Austrian practice is that we show the direct costs of ideal compliance with the protocol in obstetric visits, including the cost for all susceptible women having five tests, whereas, in practice, 97% of women had fewer than three tests. With fewer tests, that also means shorter treatment and lower treatment costs than the ideal. The average time between tests was 14 weeks, rather than the prescribed eight weeks. For two women whose infants were profoundly affected, the time between tests was 19 weeks [31]. If Austrian practice were in full compliance with the protocol, actual direct costs of screening and prenatal treatment would have been slightly higher, but the costs of treatment and accommodation of infants injured by CT and the loss of their productivity and that of their parents would have been substantially lower because fewer infants would have slipped through the screening process. The costs of screening and preventive treatment are negligible compared to the costs of treatment and accommodation for infants whose injuries are not prevented. Net benefits strongly favor screening.

**Conclusion**

As demonstrated by the Austrian national program, prenatal screening and treatment result in substantial cost saving, both from the conventional societal perspective and even from the narrow perspective of budgetary impact. Results in both cases are robust to wide variations in parameter values. Our data show the positive economic value of such a prevention measure. In summary, our findings of this economic analytic-decision model represent an important base for the discussion regarding implementation or continuation of prenatal screening for toxoplasma infection.

**Supporting information**

S1 Methods. Explanation of decision tree, clinical variables, and costs, with detailed identification of sources.

(PDF)

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S1 Methods. Explanation of decision tree, clinical variables, and costs, with detailed identification of sources.

Prusa AR, Kasper DC, Sawers L, Walter E, Hayde M, and Stillwaggon E. Congenital toxoplasmosis in Austria: Prenatal screening for prevention is cost-saving.

This decision analysis finds the lower-cost or cost-saving option. It is essentially a benefit-cost analysis in which the benefits are the savings to society and to the government budget.

Part A: Probability and cost variables in decision tree

Each node in the tree is numbered as \{number\} to guide the reader through the tree. Node numbers are indicated in Table 1, column 1, in the article.

\{1\} Decision: No screening v. Screening. In the No Screening arm, all infections and injuries are discovered at birth or in infancy, except fetal death. It is assumed that there is no prenatal screening or there is haphazard screening. All infants with CT, however, are treated; society takes on the costs of accommodating injuries, such as special schooling, and bears the societal costs of lost productivity.

\{2\} Risk of primary infections in mothers, taken from the Austrian Toxoplasmosis Register, 1992–2008 [1].

\{3\} Risk of mother-to-child transmission, taken from Austrian data, almost identical to the international estimate used in the US study [1,2]. The range of estimates considered in the US study was 0.36 to 0.61, and the intermediate value of 0.50 was used. In the present work, we are evaluating the actual Austrian experience. In untreated women in Austria, the rate of congenital transmission was 0.508, which is appropriate for the No-screening scenario.

\{4, 5, 7, 10, 13\} The probabilities are taken from the US study [2], which incorporated all the relevant international data (European and US). There are insufficient data from the Austrian experience on untreated children; the decades of data from other sources give us a better picture of the outcomes for untreated mothers and children.

\{6\} A child who has no symptoms (under the no screening scenario) will generate no costs beyond the usual well-baby care.

\{8, 9, 11, 12, 14\} These costs reflect the costs of monitoring and treating a symptomatic child, based on Austrian practice and estimates. They are net of routine well-baby care, for example routine visits in the first year.

\{8\} Visual mild = VisualMild

For mild visual disability, we assume no productivity loss for affected children or their parents.

The derivation of cost estimates is explained below in Part B.

\{9\} Visual severe = VisualMild + VisualSevere + SpecEdBlind

For children with severe visual disability, we use treatment costs for mild visual impairment, VisualMild, plus non-medical direct costs and productivity losses derived from Lafuma et al. [3], which includes child income loss and parent productivity loss.

\{11\} Visual and cognitive mild = VisualMild + CognMild + SpecEdMildCogn
Visual and cognitive severe = VisualMild + CognSevere + SpecEd SevereCogn + ParentPyLoss + ChildPyLoss

In order not to double count home care, parent productivity loss, and other non-medical costs for a child with severe visual and cognitive disability we use treatment costs for mild visual disability. Severe cognitive disability entails a child productivity loss, that is, the child is unable to work upon reaching working age, and a parent productivity loss, neither of which is included in Gustavsson et al. [4] costs for “Mental retardation,” which is used to calculate CognSevere.

Visual, cognitive, and hearing severe = VisualMild + CognSevere + HearingMild + SpecEd SevereCogn + ParentPyLoss + ChildPyLoss

Fetal or neonatal death = VSL

The cost of a fetal or neonatal death is the Value of a Statistical Life, discussed below in Part C.

No costs result for these outcomes.

If all women are screened at 8 weeks gestation, then 34% (0.344) will be IgG+, based on Austrian prevalence.

Of these IgG+ women, most will have been infected before pregnancy, and 0.000845 of women will have new infections (IgM+).

Because there were so few cases in the Austrian data, the international estimate is used [2].

For each possible outcome, the costs are listed at the terminal node (the triangle). The pattern is the same throughout. For example, at {22}, for a child with CT whose mother’s serology indicates that she was infected during the first 8 weeks of gestation and who is asymptomatic, the costs will be 1 maternal IgG test, 1 maternal IgM test, 5 infant IgG tests, 5 infant IgM tests, pediatric treatment for a year, pediatric CBC, one ECG, one cranial ultrasound, 17 fundoscopies beyond routine care, and the cost of maternal treatment when CT is identified (RxPosPCR). In {23 to 26} there are additional costs due to symptoms, including death {26}.

Loss of child productivity is not included in the screening (with pre- and post-natal treatment) arm because, in Austria, in all cases the children are able to work upon reaching working age. The Austrian Toxoplasmosis Register [1] records the specific effects in each child, so each node in the screening branch is tailored to actual experience of the children affected.

Visual impairment is mild in all children who are treated.

Visual and cognitive mild = VisualMild + CognMild

Visual and cognitive impairment is mild in all children who are treated.

Visual, cognitive & hearing with cerebral CT = VisualMild + CognMild + HearingMild + Cerebral

In this branch, there is no CT. The mother is treated for the No CT case (RxNegPCR), that is, with a negative PCR of amniotic fluid. The child is monitored for the first year and has one funduscopy at birth. There is no ECG (ECG is needed before treating infants with spiramycin and these infants will not be treated).
{28} When the mother is found to have been infected before pregnancy, the only cost is for maternal IgG and IgM. Note that in the rest of the tree, there are no maternal IgM tests because only at the 8-week test is there uncertainty about whether the maternal infection occurred during pregnancy. In actual cases, not all mothers are tested at 8 weeks. If their first test occurs at 16 weeks, they might have an IgM test, but there is no way to include that detail of non-compliance in the model. The screening costs are trivial and unimportant for determining the lower-cost outcome. The potential injuries to the child from delayed testing, however, are very important. As we note in the article, the model both understates and overstates cost of best practice (full compliance) in two ways: 1) not as many screenings are conducted as we include in the tree (overstating actual costs of screening, but understating costs of treatment for mothers identified with primary infections), and 2) children suffer injuries that might have been avoided with better compliance, and those injuries entail costs that we do include (overstating costs of injuries if compliance had been optimal).

{29} Women who are IgG– at 8 weeks are retested and 0.000845 of them will have primary infections.

{30} Risk of fetal infection based on Austrian Toxoplasmosis Register, 36/217 = 0.17.

{31, 34} Based on the Austrian Toxoplasmosis Register.

{32, 33, 35, 36, 37, 38} These costs are based on Austrian protocol and specific outcomes are based on the Austrian Toxoplasmosis Register.

{35} Visual and cognitive with cerebral CT and special schooling = VisualMild + CognMild + Cerebral + SpecEdMildCogn

{36} Visual and cognitive with cerebral CT and special schooling = VisualMild + CognMild + Cerebral

The children at nodes 35 and 36 had cerebral CT, but not all required special schooling.

{37}, {48}, {61}, {72} Visual, cognitive, and hearing = VisualMild + CognMild + HearingMild

{39} Only one funduscopy at birth is administered because there is no CT.

{40} Women negative at 16 weeks are retested at 24 weeks, of whom 0.000845 have primary infections.

{41} Based on Austrian Toxoplasmosis Register, 36/398.

{42, 45} Based on Austrian Toxoplasmosis Register.

{43, 44, 46, 47, 48, 49, 50} Based on Austrian costs and Austrian Toxoplasmosis Register.

{46} Cognitive with cerebral CT = CognMild + Cerebral

{47} Visual with physical = VisualMild +CognMild

The children at nodes 46 and 47 have mild cerebral CT or mild visual and physical impairment. None of the children in the treatment arm is unable to work.

{51} Women negative at 24 weeks are retested at 32 weeks, with 0.000845 incidence.

{52} Based on Austrian Toxoplasmosis Register, 48/368

{53, 56, 57} Based on Austrian Register
Based on Austrian protocol and costs

Cerebral CT with special schooling = CognMild + Cerebral + SpecEdMildCogn

Cerebral CT with no special schooling = CognMild + Cerebral

Visual with physical impairment = VisualMild + CognMild

When the mother is infected late in pregnancy, there is a high risk of fetal infection. Fetal infection was ruled out through PCR in 57% of cases, and the children were not treated. For late-infected women without PCR (43%), their children were treated for one year and had a year of CBC.

High risk of fetal infection with no PCR = Children are treated as a precaution.

High risk of fetal infection with negative PCR = Children are not treated.

All seronegative or unscreened mothers are tested at birth, or the newborn is tested. For simplicity, both are designated as maternal test, with the same primary infection rate of 0.000845.

Based on the Austrian Toxoplasmosis Register, 18/49 were seropositive, or 0.37.

Based on the Austrian Toxoplasmosis Register.

Based on the Austrian Toxoplasmosis Register, the protocol, and Austrian costs

Cerebral CT = CognMild + Cerebral

The mother is not treated because the test is at the time of birth. The baby is treated for one year because of high risk of transmission and has one funduscopy.

The only cost for the great majority of mothers is for the 5 IgG tests. (The number of women who remain IgG−is 1,387,680 minus 1173 primary infections.)

Part B: Derivation of costs used at terminal nodes in decision tree

Sources for the first 12 items in Table 2 are listed in the table. The following explains derivations of treatment and accommodation costs based on levels of disability and productivity losses listed in Table 2. When Austrian costs were not available, we used costs from nearby countries with similar health systems and adjusted to Austrian costs as explained below.

Cerebral CT (treatment cost, years 0 to 4) is based on the costs for “Epilepsy” from Gustavsson et al. [4] Table 7, page 730. They estimated the annual cost of epilepsy per person in Austria in 2010 to be €6,079. We adjust Austrian costs from 2010, when the consumer price index was 109.53 to 2012 when the consumer price index was 116.34 (Eurostat, “HICP (2005 = 100) – annual data (average index and rate of change),” http://ec.europa.eu/eurostat/en/web/products-datasets/-/PRC_HICP_AIND) [5]. The ratio is 1.062, that is, consumer prices rose 6.2% in Austria between 2010 and 2012. Adjusting to Austrian prices in 2012, the annual cost is

€6,079 x 1.062 = €6,457.

Since these children have relatively mild outcomes and their symptoms are controlled, we apply these costs only for 5 years. Total cost for 5 years discounted at 3% annually is €30,458. Our analysis estimates the value of a stream of economic costs into the future. Future costs are assumed to be worth less than current ones, so costs and benefits in the future must be weighted less than those in the near term to
determine what economists call the present discounted value. The annual rate of discount most commonly used in health economics is 3% [6].

**Child productivity loss** is the life-time wage loss due to severe impairment that prevents gainful employment. The OECD reports the mean Austrian annual wage for full-time, full-year employees for 2012 to be €38,273, (OECD.Stat, “Average Annual Wage,” [https://stats.oecd.org/Index.aspx?DataSetCode=AV_AN_WAGE](https://stats.oecd.org/Index.aspx?DataSetCode=AV_AN_WAGE)) [7]. The mean retirement age in Austria reported by the OECD ("Ageing and Employment Policies – Statistics on average effective age of retirement,” [http://www.oecd.org/els/emp/ageingandemploymentpolicies-statisticsonaverageeffectiveageofretirement.htm](http://www.oecd.org/els/emp/ageingandemploymentpolicies-statisticsonaverageeffectiveageofretirement.htm)) [8] is 60.5 years. The total wage loss from age 18 to age 60.5 discounted at 3% annually is €561,721.

**Cognitive mild (direct and indirect costs)** is derived from Gustavsson et al. [4] Table 11, page 734, which gives annual cost per person as weighted means for all diagnoses and age groups within the disorder. For this category we use “Child and adolescent disorders,” which covers several developmental disorders, and includes direct and indirect costs. Indirect costs for this category include parent productivity loss. Gustavsson et al. estimate the annual cost of child and adolescent disorders for Austria in 2010 to be €4,391. We adjust to 2012 prices,

\[
€4,391 \times 1.062 = €4,664.
\]

The total cost of mild cognitive impairment over 18 years discounted at 3% annually is €66,071.

**Cognitive severe (direct costs and some indirect costs, lifetime)** is based on Gustavsson et al. [4] Table 11, page 734. Their estimate of the cost of “Mental retardation” includes direct and some indirect costs but does not include lifetime productivity loss for the parent or for the child upon reaching working age. For Austria in 2010, Gustavsson et al. estimate an annual cost of €13,404. Adjusting to 2012 prices, annual cost of mental retardation in 2012 in Austria is

\[
€13,404 \times 1.062 = €14,237.
\]

Life expectancy in Austria is 80.5 years (OECD, “Life expectancy has increased remarkably in OECD countries,” [www.oecd.org/berlin/47570143.pdf](http://www.oecd.org/berlin/47570143.pdf)) [9]. The lifetime costs of mental retardation discounted at 3% annually are €445,536.

**Hearing mild (treatment cost, lifetime)** Hearing loss is not seen in children with CT in the absence of other outcomes. Even though hearing loss might be profound, we estimate the cost only for mild hearing loss (correctable with hearing aid) in order to avoid double counting for special schooling, parental productivity loss, and other treatment and indirect costs. Thus we include only the cost of hearing aids, which in Belgium, without subsidies, is €3,500 (Hear-it, at [http://www.hear-it.org/hearing-loss-Belgium](http://www.hear-it.org/hearing-loss-Belgium)).

Hearing aids need to be replaced every five years (Emory University, [http://www.emoryhealthcare.org/ear-nose-throat/audiology/faq-hearing-aids.html](http://www.emoryhealthcare.org/ear-nose-throat/audiology/faq-hearing-aids.html), and Hear-it, [http://www.hear-it.org/hearing-loss-Denmark](http://www.hear-it.org/hearing-loss-Denmark)). We do not include the cost of batteries or hearing tests. We adjust for the difference in consumer price levels between Belgium and Austria in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100),” ([http://ec.europa.eu/eurostat/tgm/printTable.do?tab=table&plugin=1&language=en&pcode=tec00120&printPreview=true](http://ec.europa.eu/eurostat/tgm/printTable.do?tab=table&plugin=1&language=en&pcode=tec00120&printPreview=true)) [10]. Adjusting to the Austrian price level, the cost in 2012 is:

\[
€3500 \times 0.0962 = €3,366.
\]

The total cost for hearing aids replaced every five years beginning at age 2 until age 77 discounted at 3% annually is €20,924.
Parent productivity loss (years 0 to 18) is based on estimates of mother’s work reduction from Lange et al. [11] Tables 1 and 2, page 1131, calculated in Walter et al. [12] Table 7.9, page 134. Walter et al. estimate the mother’s annual earnings loss for Germany in 2008, for children < 6 years, 6 to 10 years, and 11 to 18 years. We adjust from German to Austrian prices for 2008 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10]. Austrian prices were 1.0154 higher than German prices in 2008. We adjust Austrian costs to the price level in 2012 using Eurostat, “HICP (2005 = 100) - annual data (average index and rate of change)” [5]. Austrian prices increased 8.45% between 2008 and 2012.

We adjust each of the annual earnings loss estimates for Germany in 2008 to Austrian prices in 2012, as follows:

- < 6 years: \[€3,418.58 \times 1.0154 \times 1.0845 = €3,764.54\]
- 6 to 10 y: \[€2,084.36 \times 1.0154 \times 1.0845 = €2,295.30\]
- 11 to 18 y: \[€672.34 \times 1.0154 \times 1.0845 = €740.38\]

The total parental earnings loss over 18 years discounted at 3% annually is €33,940.

Special Ed, severe visual impairment is based on a study by Walter et al. [12] Table 7.9, page 134. They estimate the cost of schooling for blind children in Germany in 2008 to be €10,333 per year for 10 years. We adjust that amount to Austrian prices in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5], for an estimate of annual per-child cost of special schooling of

\[€10,333 \times 1.0154 \times 1.0845 = €11,379\]

Assuming children have special schooling from age 5 to 14, total schooling cost discounted at 3% annually is €86,239.

Special Ed, mild cognitive impairment is based on a study by Walter et al. [12] Table 7.9, page 134. They estimate annual costs of schooling in Germany in 2008 for those with mild cognitive impairment to be €6,126. We adjust German schooling costs in 2008 to Austrian prices in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5], as follows:

\[€6,126 \times 1.0154 \times 1.0845 = €6,746\]

The children receive 15 years of special schooling from age 4 to 18. Total costs are discounted at 3% annually and amount to €73,699.

Special Ed, severe cognitive impairment is based on a study by Walter et al. [12] Table 7.9, page 134. They estimate the cost of schooling for children with severe cognitive impairment in Germany in 2008 to be €44,835 per year for 20 years. We adjust that amount to Austrian prices in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5], for an estimate of annual per-child cost of special schooling of

\[€44,835 \times 1.0154 \times 1.0845 = €49,372\]

Assuming the children receive special schooling from age 2 to 21, total costs for 20 years discounted at 3% annually amount to €713,141.
Visual mild (treatment cost only, age 0 to 18) is based on a study by Walter et al. [12] Table 7.6 and 7.7, pages 130–131. They give estimates of treatment costs for visual impairment in children with CMV who were either symptomatic or asymptomatic at birth, assuming a 5% annual discount rate. Averaging those two estimates gives the following treatment costs of visual impairment as

$$\text{€1,258} + \text{€1,222} = \text{€2,480}/2 = \text{€1,240}.$$  

To determine the treatment costs with the 3% annual discount rate that is used throughout our study, we calculate the annual cost of treatment, assuming that costs per year are uniform from age 0 to 18, using the following formula

$$\text{Annual cost} = \frac{[1240 \times (1 + r)^{Y-1} r]}{[1 + r]^Y - 1},$$

where \( r \) is the annual discount rate and \( Y \) is the year.

The annual treatment cost that would produce a total cost of €1,240 for 18 years discounted at 5% is €100.03. The formula for deriving the annual expenditure from a discounted present value can be found at moneychimp (http://www.moneychimp.com/articles/finworks/fmpayout.htm), which also provides an annuity calculator (http://www.moneychimp.com/calculator/annuity_calculator.htm).

We adjust the German costs in 2008 to Austrian prices in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5], producing the following estimate of annual treatment costs in Austria:

$$\text{€100.03} \times 1.0154 \times 1.0845 = \text{€111.25}.$$  

Total Austrian treatment cost over 18 years discounted at 3% annually is €1,576.

Visual severe (non-medical costs) is composed of two separate costs, the loss of earnings from severe visual impairment and other non-medical costs associated with severe visual impairment. These costs must be calculated separately since they occur at different periods over a person’s lifetime. Estimates of both costs are based on a study of visual impairment in four European countries by Lafuma et al. [3]. In Table II, page 199, they report estimated annual per person income loss from severe visual impairment in Germany in 2004 to be

$$\text{€3,705.14} + \text{€137.23} = \text{€3,842}.$$  

The calculation of lifetime earnings loss from severe visual impairment assumes people work from age 18 to the mean retirement age of 60.5 in Austria (OECD, “Ageing and Employment Policies – Statistics on average effective age of retirement”) [8]. We adjust average annual German income loss in 2004 to Austrian prices in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5], and find annual earnings loss from severe visual impairment in Austria in 2012 to be

$$\text{€3,842.37} \times 0.9857 \times 1.18787 = \text{€4,499}.$$  

Total income loss for ages 18 to 60.5 discounted at 3% annually is €66,030.

Again using Lafuma et al. [3] Table II, page 199, we determine the costs of severe visual disability other than loss of earnings by subtracting the cost of lost earnings from total annual, per person societal costs (including unmet needs)
\[ \text{€12,783.04} - \text{€3,842.37} = \text{€8,940.67}. \]

We adjust annual German costs in 2004 of disability from severe visual impairment excluding income loss to estimate Austrian costs in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5]. Non-medical costs arising from severe visual impairment excluding earnings loss in Austria in 2012 are thus

\[ \text{€8,940.67} \times 0.9857 \times 1.18787 = \text{€10,468}. \]

Total other non-medical costs excluding earnings loss for all persons with severe visual impairment age 0 to 80.5, the expected life-span of Austrians (OECD, “Life expectancy has increased remarkably in OECD countries” [9]) discounted at 3% annually are €327,594.

Total non-medical costs (including earnings loss during working years) are the sum of the two figures calculated above, the loss of earnings from age 18 to 60.5 and other non-medical costs incurred over the lifetime:

\[ \text{€66,030} + \text{€327,594} = \text{€393,624}. \]

**Part C: Value of a Statistical Life**

Measures of the value of a statistical life (VSL) are routinely used in the economic evaluation of public policies that may lead to higher or lower mortality. As a recent publication of the Organization of European Cooperation and Development (OECD) put it, “policy makers are regularly devising policies and regulations that affect people’s risk of death and that seek to protect lives in society, and require methodologies for comparing the costs of reducing risk with the expected benefits in terms of lives saved. The benefits of prevented mortalities can be expressed in terms of a ‘Value of a Statistical Life’ (VSL), which represents the value a given population places *ex ante* on avoiding the death of an unidentified individual” (from the Foreword of [13]).

There is a voluminous literature on measuring VSL in Europe and other industrialized countries [13-16]. Initially, the discourse over VSL typically employed a human capital approach to measuring VSL based on the estimated value of income over a lifetime. The human capital approach has been supplanted by the stated preference approach favored by most European economists and the revealed preference approach used by most US economists. The latter two methodologies produce substantially higher measures of VSL than the human capital approach.

The OECD recently assessed over 800 studies that use the stated preference approach to measuring VSL [13]. That meta-analysis found quality-screened measures of VSL ranging between US $1.8–5.4 million (in 2005 US dollars) with median and mean of US $3.6 million. The OECD recommends accepting the mean/median figure as the “base value” to be adjusted for the purposes of estimating the VSL for the particular group under consideration (page 127 in [13]). They add, “when the policy that is analysed targets children specifically (or affects mainly children), a higher VSL for children is recommended, based on the available empirical evidence from the United States and Europe. VSL for children should be 1.5-2.0 times higher than the mean adult VSL” (page 131 in [13], emphasis in original).

Five studies measured VSL in Austria [17-21]. In the last quarter century, substantial progress has been made in the methodology of measuring VSL, and only three of the five studies were carried out since the 1980s. Two of the recent measures of VSL in Austria lie within the OECD’s range of VSL of US $1.8–5.4 million (in 2005 US dollars) [19,20], and the third is just below that range [21]. Rather than base our
statistical analysis on three studies, we opt to follow the OECD’s recommendation since it is based on hundreds of studies.

We adjust OECD’s recommendation for VSL, stated in US dollars in 2005, to the price level in Austria in 2012 using Eurostat, “Comparative price levels of final consumption by private households including indirect taxes (EU 28 = 100)” [10] and “HICP (2005 = 100) - annual data (average index and rate of change)” [5]. Exchange rate data are taken from OANDA (http://www.oanda.com/currency/average/).

At present, most US economists measure VSL using a revealed preference approach based on income differentials among occupations with different mortality risks. Datasets that have recently become available in the United States allow much more precise measures of income and mortality risk by occupation, industry, gender, age, and other categories. The new data lead to measures of VSL that are typically higher than both the earlier measures using the revealed preference approach and current measures using the stated preference approach, which is commonly used in Europe [22]. Recent US government benefit-cost analyses use measures of adult VSL that range between US$6 million and US$10 million (in 2013 dollars), equivalent to €4.6–€7.7 million in 2012 euros [23]. In the United States, several authors discourage upward adjustment of VSL for children [24]. In short, the US and European approaches to VSL, though they use different methodologies and different age adjustments, arrive at recommended measures of VSL that are remarkably similar (€5–€6.7 million in Europe vs. €4.6–€7.7 million in the United States).

We use productivity losses derived from the literature as explained in Part B for surviving children with vision, hearing, or cognitive impairment. None of those estimates is adequate for attributing a value to fetal or neonatal death, which is why we use VSL in those few cases [25].

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