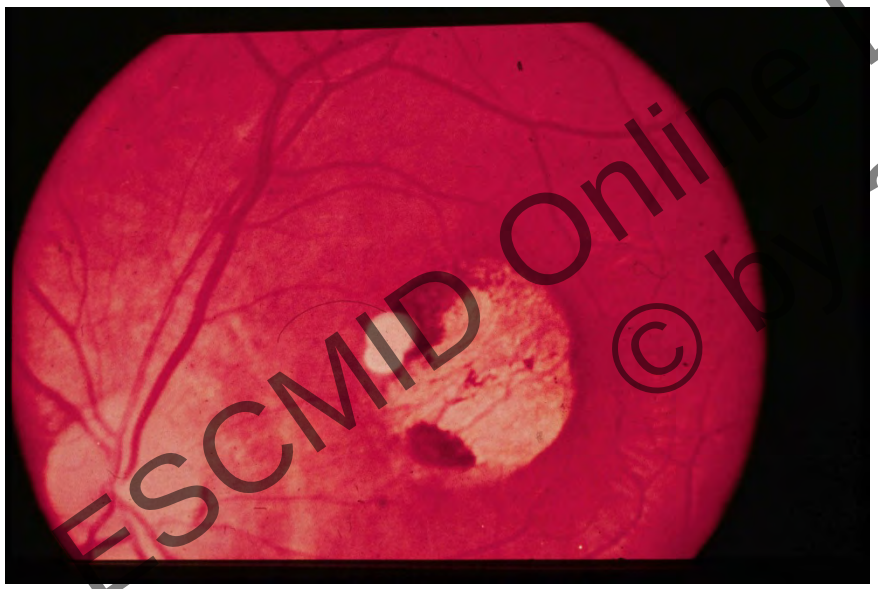
Screening for Congenital Toxoplasmosis – pro's and con's



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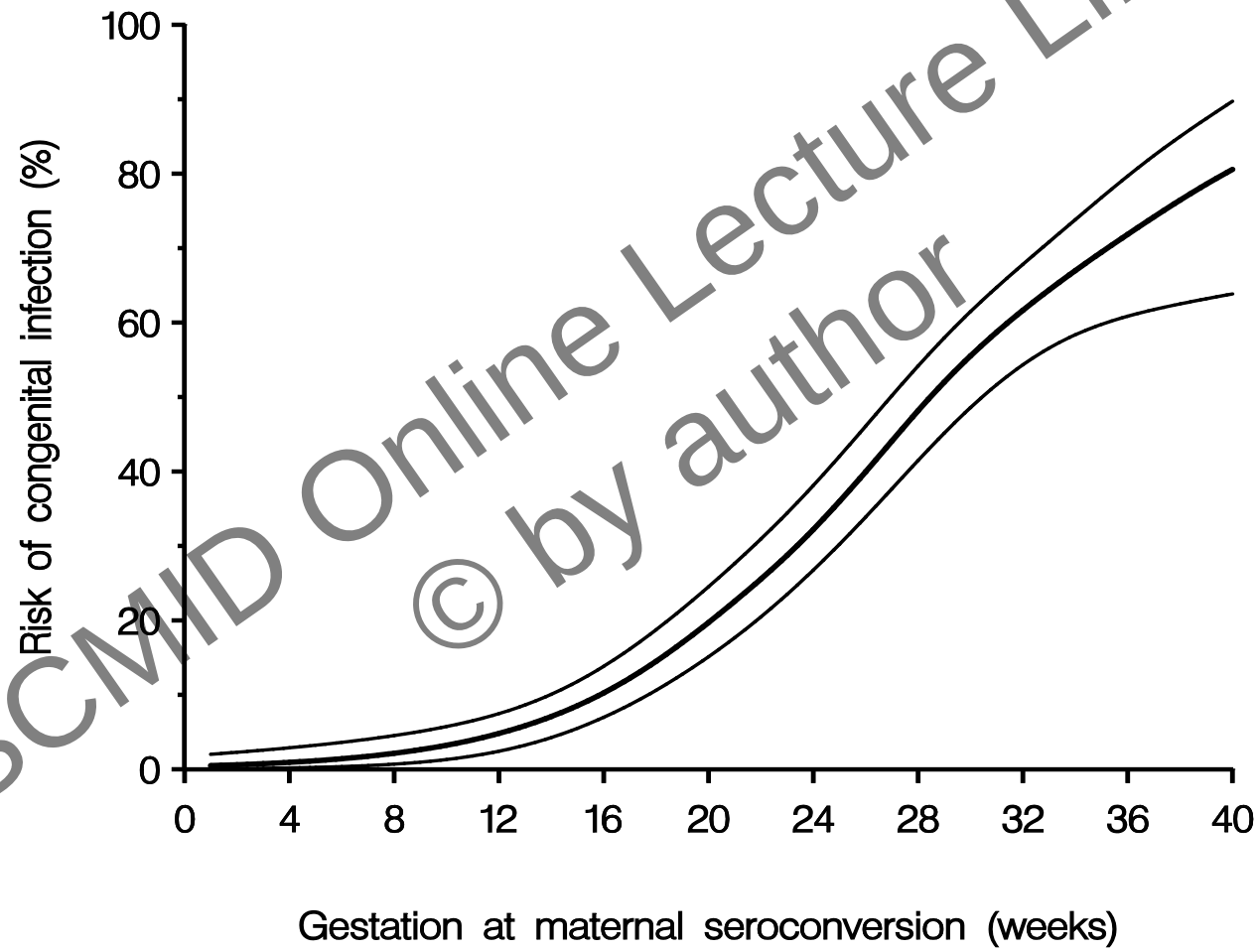
Danish Neonatal Toxoplasma

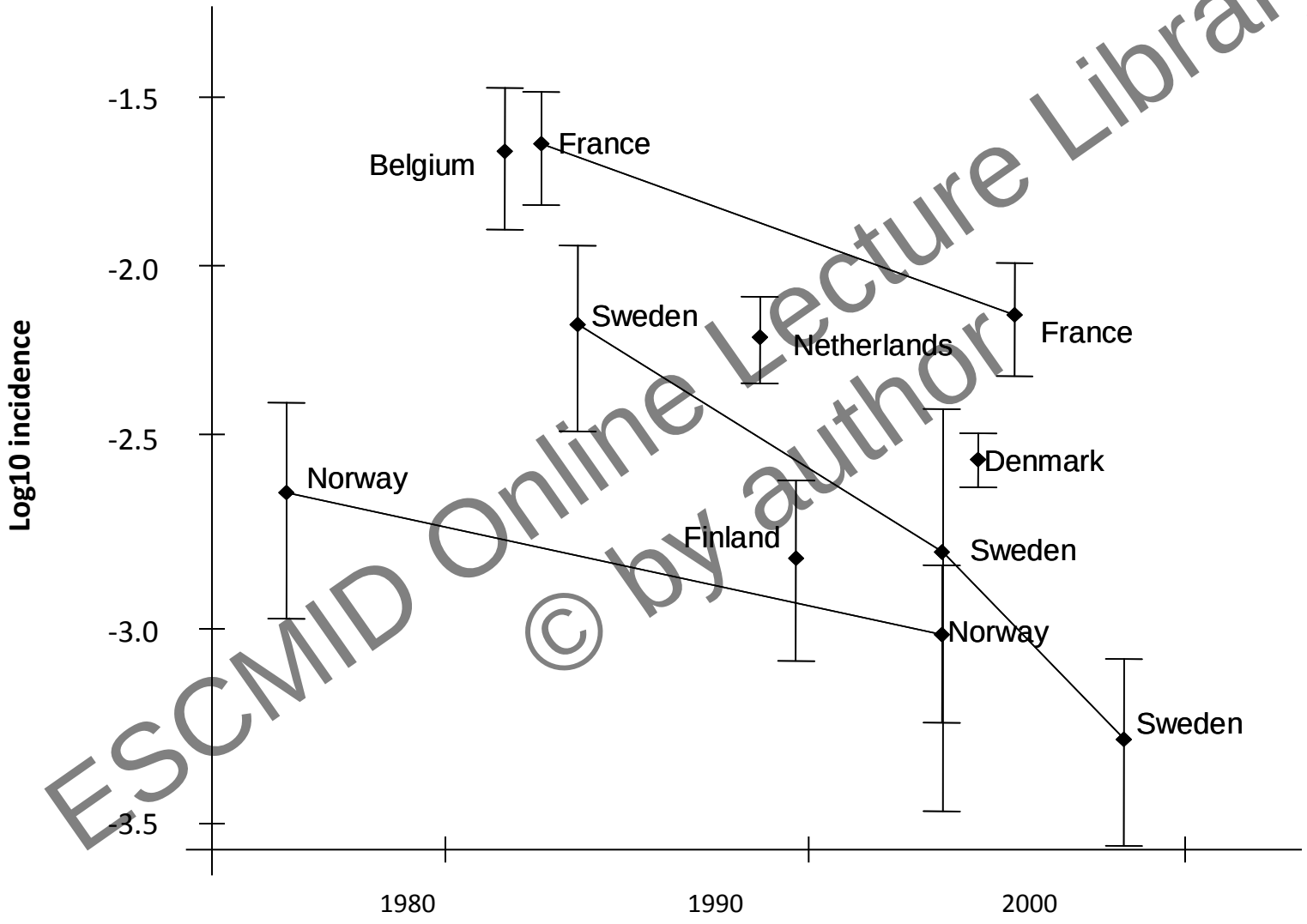
Screening Program 1999 - 2003

Transmission of Toxoplasma and gestational age



Dunn et al, Lancet 1999;353;1829-33.

European Incidence studies based on seroconversion, with 95% CI, plotted against time of the survey.



Based on a synthesis of seroprevalence, seroconversion, and IgM prevalence information

Welton & Aedes *JRSS (C) Applied Statistics* 2005;54:385-404

ORIGINAL ARTICLE

The national neonatal screening programme for congenital toxoplasmosis in Denmark: results from the initial four years, 1999–2002

D R Schmidt, B Hogh, O Andersen, J Fuchs, H Fledelius, E Petersen

Arch Dis Child 2006;91:661–665. doi: 10.1136/adc.2004.066514

Table 1 Number of infants tested per year and the number who tested anti-toxoplasma antibody positive at the screening test and at the confirmatory test

Year	1999	2000	2001	2002	Total
Number of infants tested	66232	67081	65450	64149	262912
Positive PKU-card	35	22	25	14	96
Positive serum sample	11	13	19	12	55

Adverse events during treatment

Neutropenia, elevated liver enzymes, trombocytose

Follow-up on 37 children:

- 31 of 37 (83.8%) children received 3 months continuous S/P treatment. 13 of 37 (35.1%) had side effects, no change in treatment.
- 2 of 37 (5.4%) children had interruptions during treatment due to side effects.
- 4 of 37 (10.8%) children had treatment discontinued due to side effects.
- TOTAL 19/37 (51.4%) experienced side effects during the recommended 3 month S/P treatment

Schmidt et al. Arch Dis Child 2009

J Inherit Metab Dis (2010) 33 (Suppl 2):S241–S247
DOI 10.1007/s10545-010-9124-4

NEWBORN SCREENING

Congenital toxoplasmosis—a report on the Danish neonatal screening programme 1999–2007

Dennis Röser · Henrik Vedel Nielsen · Eskild Petersen · Peter Saugmann-Jensen · Peter Bent Nørgaard-Pedersen

Röser et al. J Inherit Metab Dis 2010;33(Suppl.2):241-7

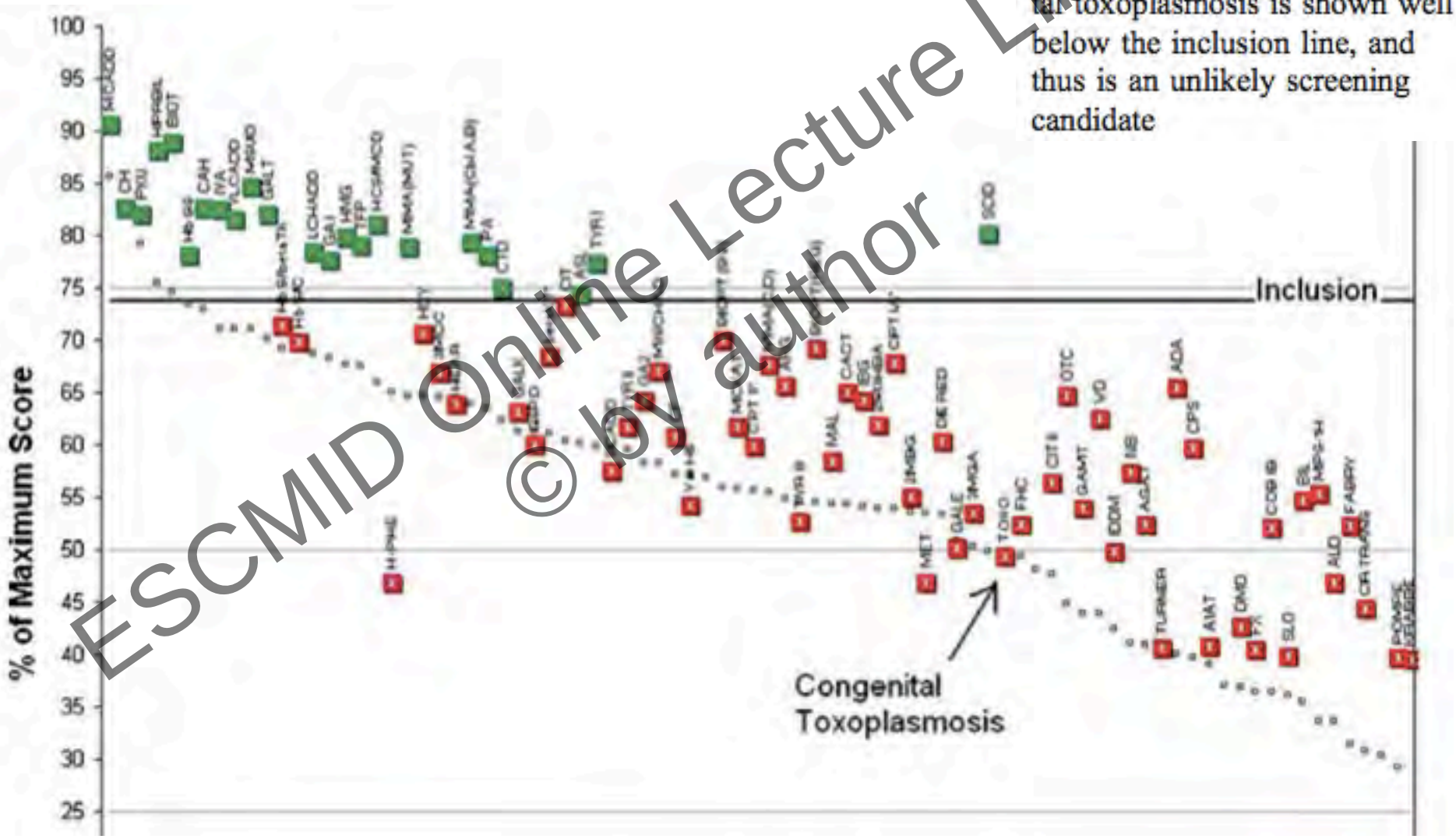


Fig. 2 Distribution of candidates for newborn screening using the Danish adaptation of the ACMG Uniform Screening Panel (ACMG 2006). Congenital toxoplasmosis is shown well below the inclusion line, and thus is an unlikely screening candidate

Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data

Lancet 2007; 369: 115–22

*The SYROCOT (Systematic Review on Congenital Toxoplasmosis) study group**

22 cohorts included. Individual data from 1.438 mothers giving birth to 398 *Toxoplasma*-infected children

	OR (95% CI)	p
Timing of prenatal treatment initiation		0·05
<3 weeks after seroconversion (n=312)	0·48 (0·28–0·80)	
>3 weeks and <5 weeks after seroconversion (n=442)	0·64 (0·40–1·02)	
>5 weeks and <8 weeks after seroconversion (n=360)	0·60 (0·36–1·01)	
≥8 weeks after seroconversion (n=324)	Ref	
Type of treatment (spiramycin *vs* PS)	0·79 (0·55–1·13)	0·19
Gestational age at maternal seroconversion (per week)	1·15 (1·12–1·17)	<0·0001
Latitude (for 5° higher)	0·71 (0·53–0·96)	0·03
Start of study period		0·14
After 1994	0·39 (0·15–1·05)	
Between 1991 and 1994	0·46 (0·17–1·21)	
Before 1991	Ref	

Model adjusted for gestational age at maternal seroconversion estimated by the integrated maximum likelihood method. PS=pyrimethamine-sulphonamide.

Table 2: **Adjusted effect of the timing and type of prenatal treatment on the risk of mother-to-child transmission in European prenatal screening centres in subsample of treated mothers (n=1438 mothers, 398 infected children)**

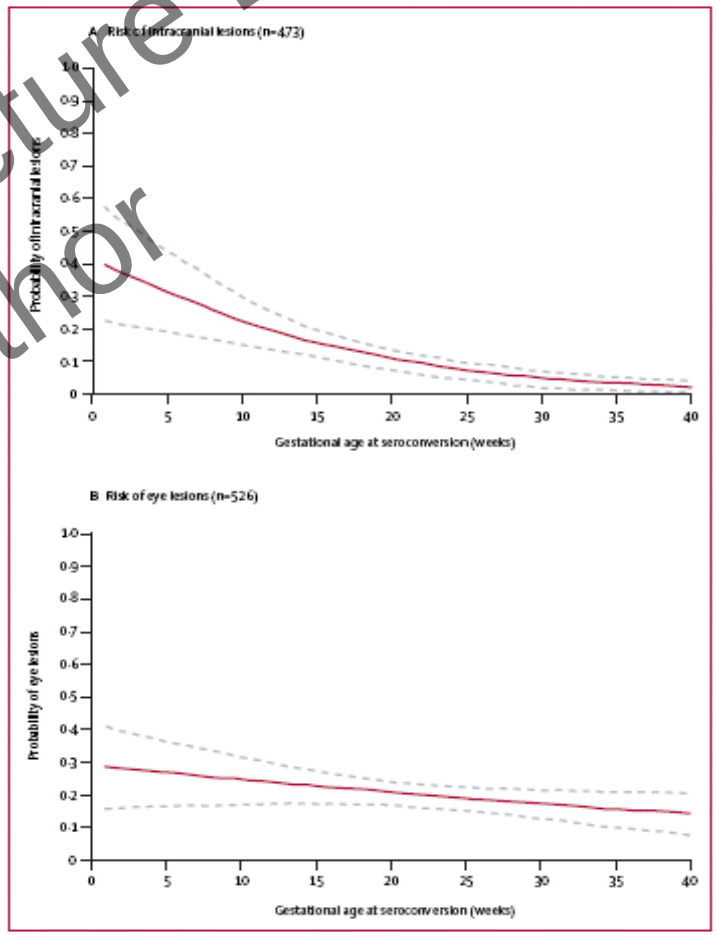
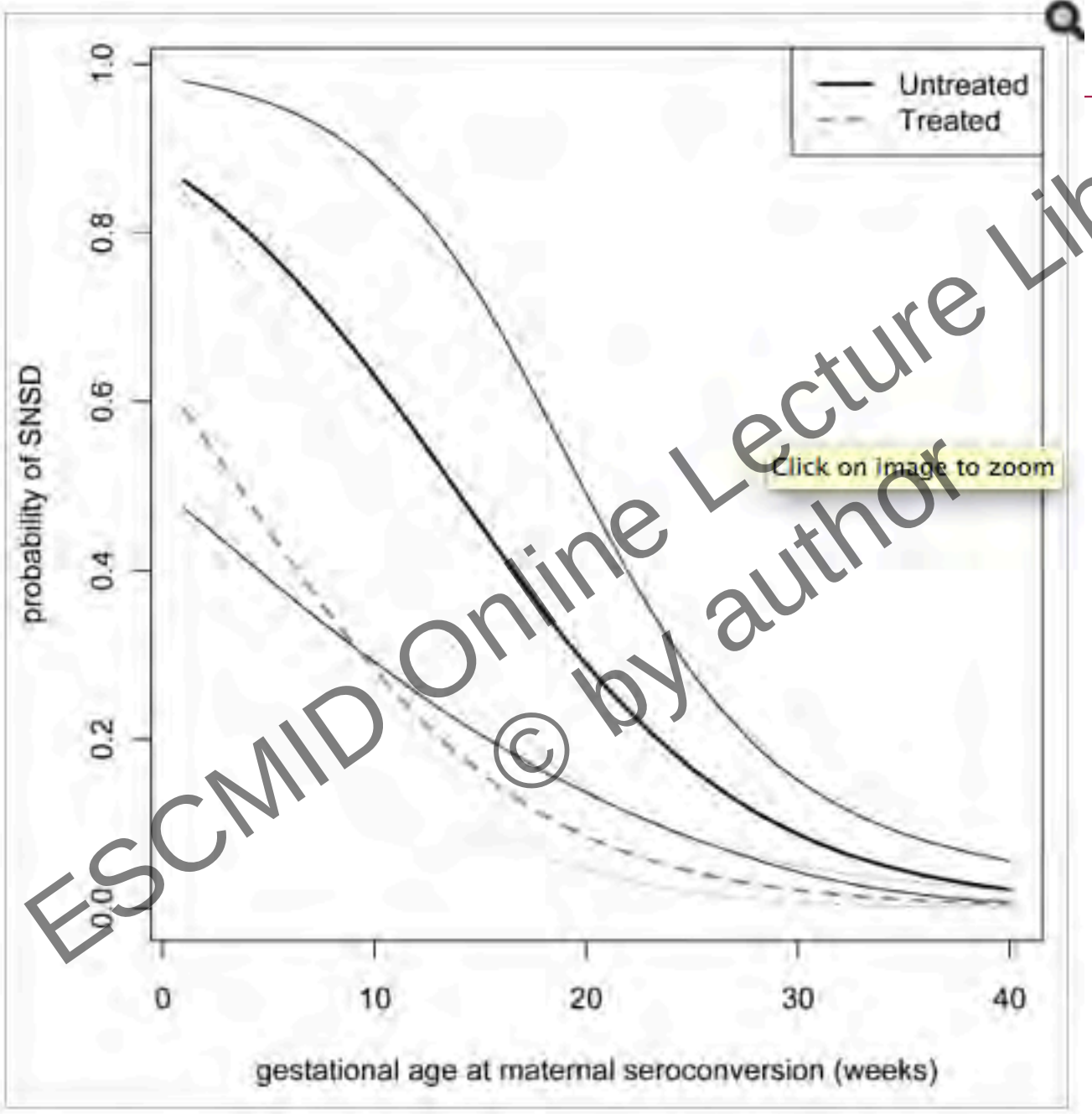


Figure 3: Risk of clinical manifestations in children infected by T gondii by gestational age at maternal seroconversion
Dotted lines are bounds of 95% CI.



Prenatal treatment for serious Neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study.
Cortina-Borja M et al. & EMSCOT.
PLoS Med. 2010 Oct 12;7(10).

Outcome of Treatment for Congenital Toxoplasmosis, 1981–2004: The National Collaborative Chicago-Based, Congenital Toxoplasmosis Study

Rima McLeod,[1,2,3,5,7,8] Kenneth Boyer,[9,11] Theodore Karrison,[4] Kristen Kasza,[4] Charles Swisher,[12] Nancy Roizen,[3,6,a] Jessica Jalbrzikowski,[1] Jack Remington,[15,16] Peter Heydemann,[9,10] A. Gwendolyn Noble,[13] Marilyn Mets,[13] Ellen Holfels,[8,a] Shawn Withers,[14] Paul Latkany,[17,18] and Paul Meier,[19] for the Toxoplasmosis Study Group[b]

CID 2006;42:1383–94

Table 7. Episodes of reversible neutropenia requiring temporary withholding of medications.

Treatment arm	No. of episodes during which medication was withheld, mean ± SD (range)	No. of patients who stopped medication/no. in cohort who have completed 1 year of therapy (%)			No. of patients who discontinued treatment ⩾4 times because of neutropenia
		Feasibility	Randomized	All	
1	2 ± 1 (1–4)	6/14 (43)	15/43 (35)	21/57 (37)	2
2	3 ± 3 (1–11)	8/21 (38)	12/38 (32)	20/59 (34)	7

Treatment was as follows. Daily doses of pyrimethamine (1 mg/kg) were administered for either 2 months (treatment 1) or 6 months (treatment 2); thereafter this dose was received only on Mondays, Wednesdays, and Fridays for the remainder of 1 year. Sulfadiazine (100 mg/kg/day, divided into 2 doses) was also administered for 12 months, and leukovorin was administered for 12 months. Medications for children receiving treat-

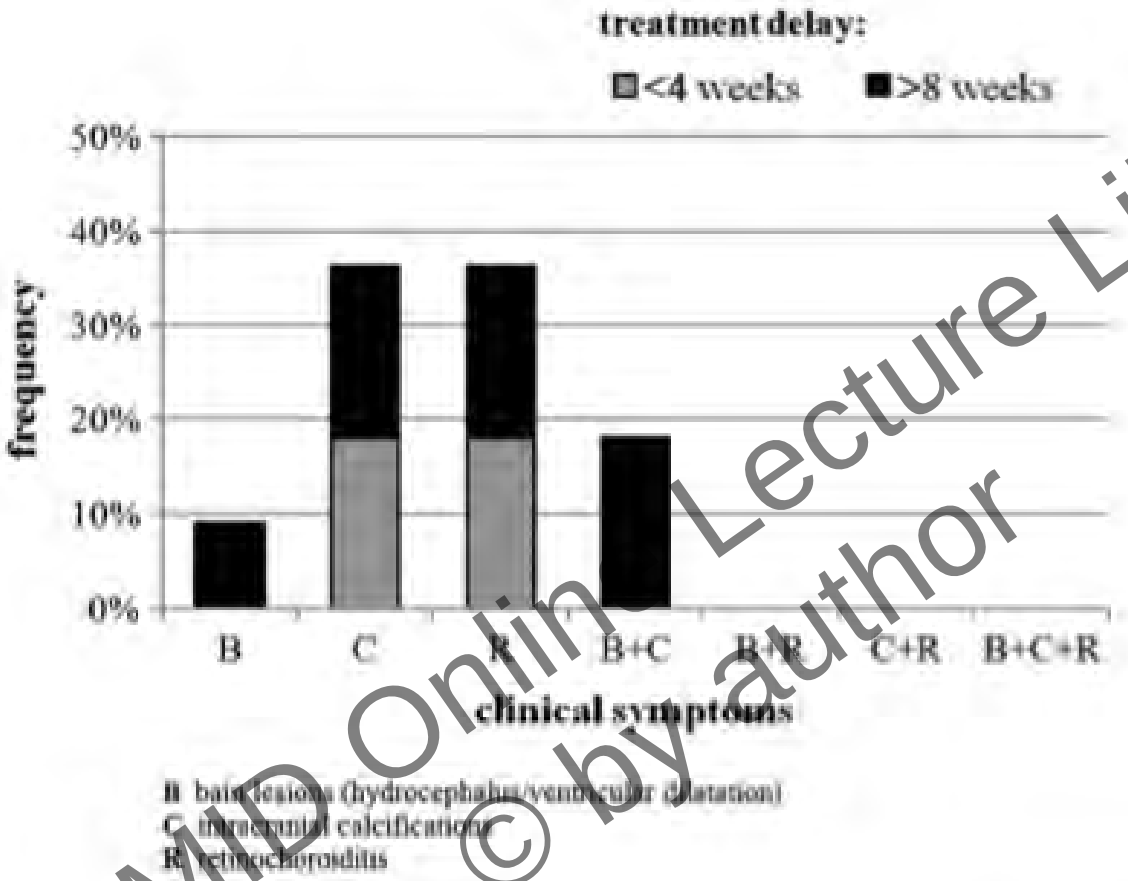


Figure 6. Frequency of clinical symptoms in infected newborns. B, brain lesions (hydrocephalus/ventricular dilatation); C, intracranial calcifications; R, retinochoroiditis. Cumulative percentages are given.

Hotop et al. CID 2012;54:1545

Conclusion

Both the US and EU studies find a benefit of treatment in children with neurological sequelae at birth.

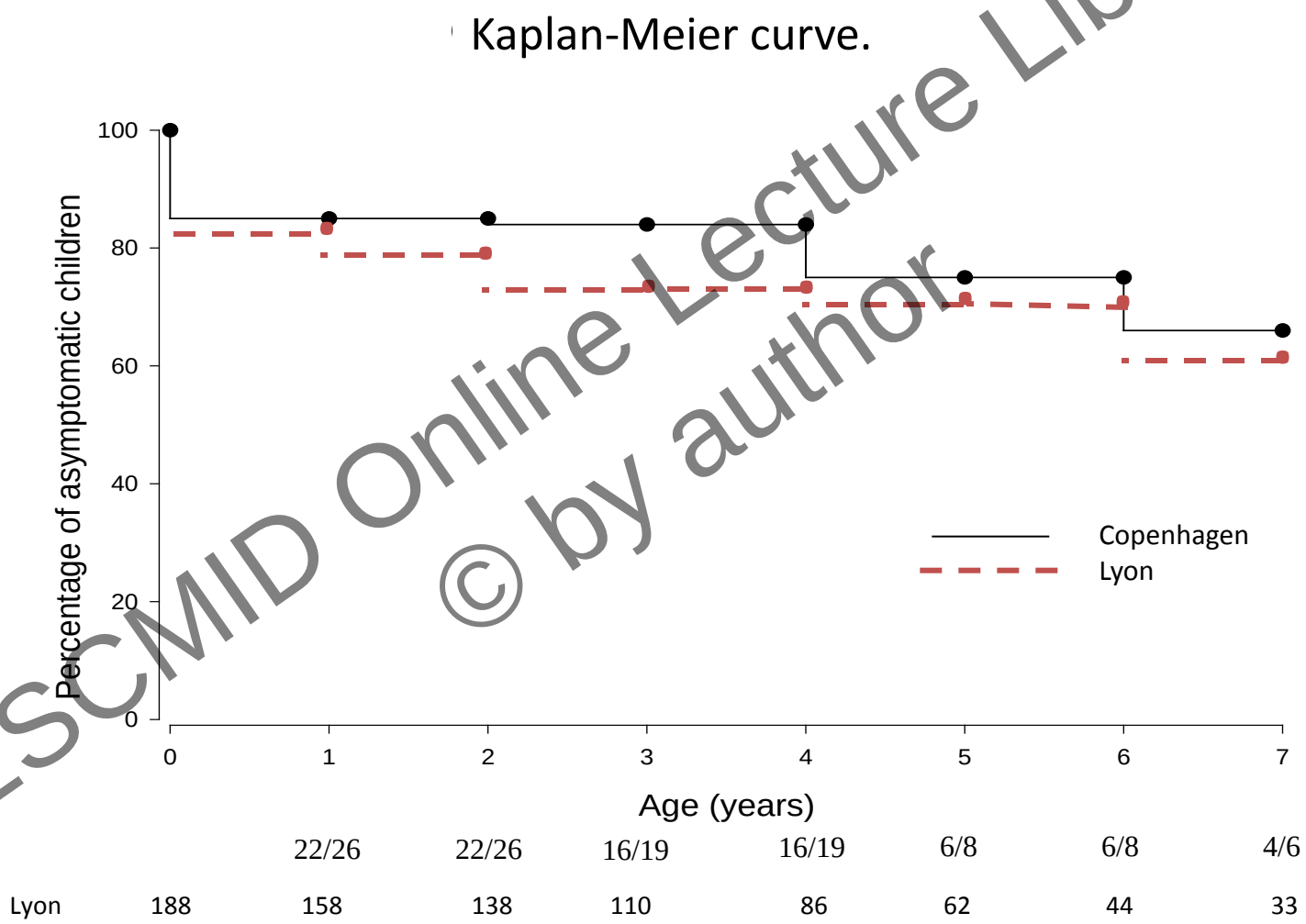
But

The majority – 70% to 80% - are asymptomatic at birth

Does asymptomatic children benefit from treatment ?

SYROCOT found decreasing effect with increasing gestational age

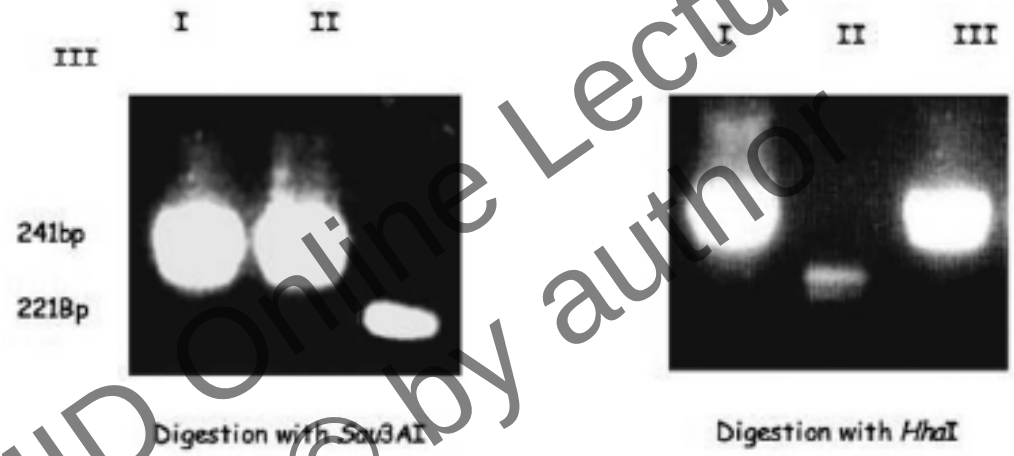
Chorioretininal lesions after 12 vs. 3 months treatment



Petersen E and Peyron F: Unpublished

T. gondii genotypes from patient with eye disease in Brazil

PCR RFLP analysis of SAG2 from enucleated eyes



Out of 92 eyes, 11 was PCR positive for *T.gondii SAG2*, and all were genotype I

Vallochi et al. Am J Ophthalmol 2005;139:350-1

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Ocular Sequelae of Congenital Toxoplasmosis in Brazil Compared with Europe

Ruth E. Gilbert[1]*, Katherine Freeman[2], Eleonor G. Lago[3], Lilian M. G. Bahia-Oliveira[4], Hooi Kuan Tan[1], Martine Wallon[5], Wilma Buffolano[6], Miles R. Stanford[7], Eskild Petersen[8], for The European Multicentre Study on Congenital Toxoplasmosis (EMSCOT)

Citation: Gilbert RE, Freeman K, Lago EG, Bahia-Oliveira LMG, Tan HK, et al. (2008) Ocular Sequelae of Congenital Toxoplasmosis in Europe. PLoS Negl Trop Dis 2(8): e277. doi:10.1371/journal.pntd.0000277

Figure 1. Survival analyses showing proportion of children without retinochoroiditis according to age in years when first eye lesion was detected in Brazil (solid line), and European neonatal (long dash) and prenatal centers (short dash).
doi:10.1371/journal.pntd.0000277.g001

OPEN ACCESS Freely available online

PLoS one

Genetic and Epigenetic Factors at *COL2A1* and *ABCA4* Influence Clinical Outcome in Congenital Toxoplasmosis

Sarra E. Jamieson[1¤], Lee-Anne de Roubaix[1], Mario Cortina-Borja[2], Hooi Kuan Tan[2], Ernest J. Mui[3], Heather J. Cordell[1,4], Michael J. Kirisits[3], E. Nancy Miller[1], Christopher S. Peacock[1], Aubrey C. Hargrave[3], Jessica J. Coyne[3], Kenneth Boyer[5], Marie-Hélène Bessieres[6], Wilma Buffolano[7], Nicole Ferret[8], Jacqueline Franck[9], François Kieffer[10], Paul Meier[11], Dorota E. Nowakowska[12], Malgorzata Paul[13], François Peyron[14], Babill Stray-Pedersen[15], Andrea-Romana Prusa[16], Philippe Thulliez[17], Martine Wallon[14], Eskild Petersen[18], Rima McLeod[3], Ruth E. Gilbert[2], Jenefer M. Blackwell[1¤*]

Methods and Findings: In 457 mother-child pairs from Europe, and 149 child/parent trios from North America, we show that ocular and brain disease in congenital toxoplasmosis associate with polymorphisms in *ABCA4* encoding ATP-binding cassette transporter, subfamily A, member 4. Polymorphisms at *COL2A1* encoding type II collagen associate only with ocular disease. Both loci showed unusual inheritance patterns for the disease allele when comparing outcomes in heterozygous affected children with outcomes in affected children of heterozygous mothers. Modeling suggested either an effect of

Jamieson et al. PLoS One 2008;3(6):e2285

Intervention	No intervention
Symptomatic children benefit from treatment early in pregnancy	70% to 80% asymptomatic
Non-gentotype II prevalent	Genotype II dominant
Side effects	No side effects
Parental anxiety	No parental axiety
Treatment < 3 weeks of infection Prevention of transmission Treatment < 3 weeks of infection	No
Neonatal screening ? More severe cases diagnosed	Some severe cases diagnosed

How do we prevent transmission ?

Screening with short intervals for instance every 2 weeks

Home testing with point of care test for instance detecting

***Toxoplasma*-specific IgG**

- Thank you very much -