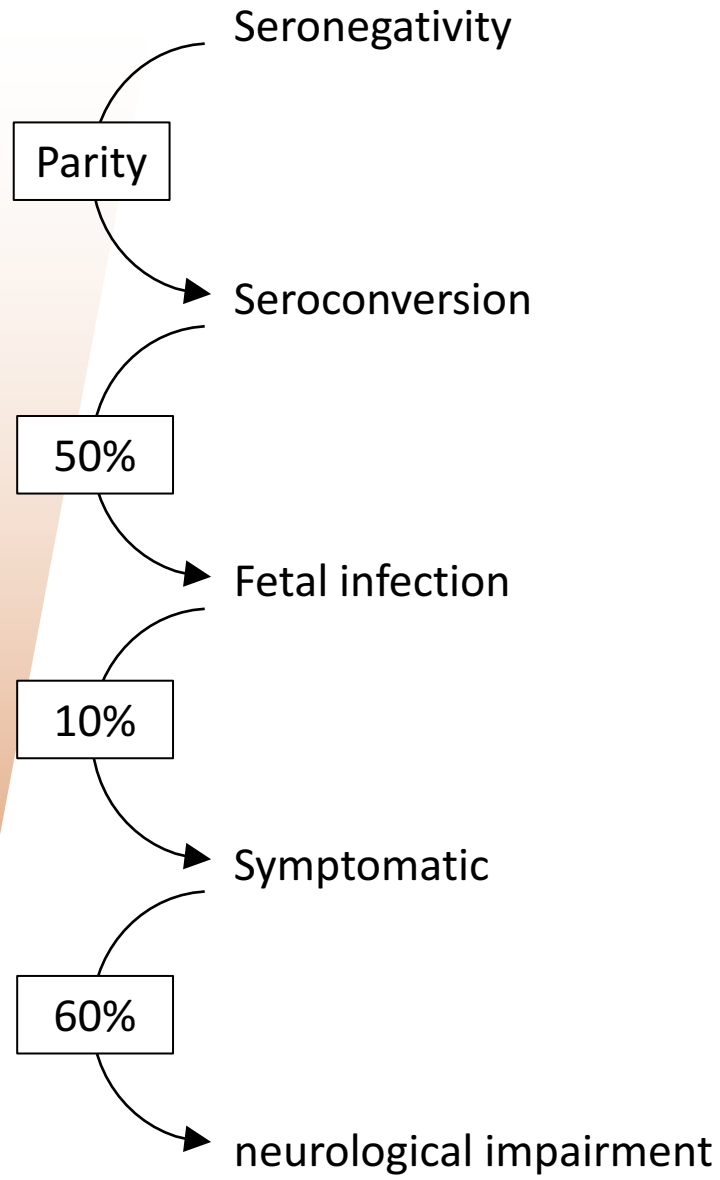


CMV en France

0,37% * nouveau-nés infectés	2960/an
12,7% symptomatiques	376/an
60% avec déficit cognitif ± auditif	225/an
87,3% asymptomatiques	2584/an
13,5%** avec déficit auditif	349/an

Seronegativity

Parity

Seroconversion

50%

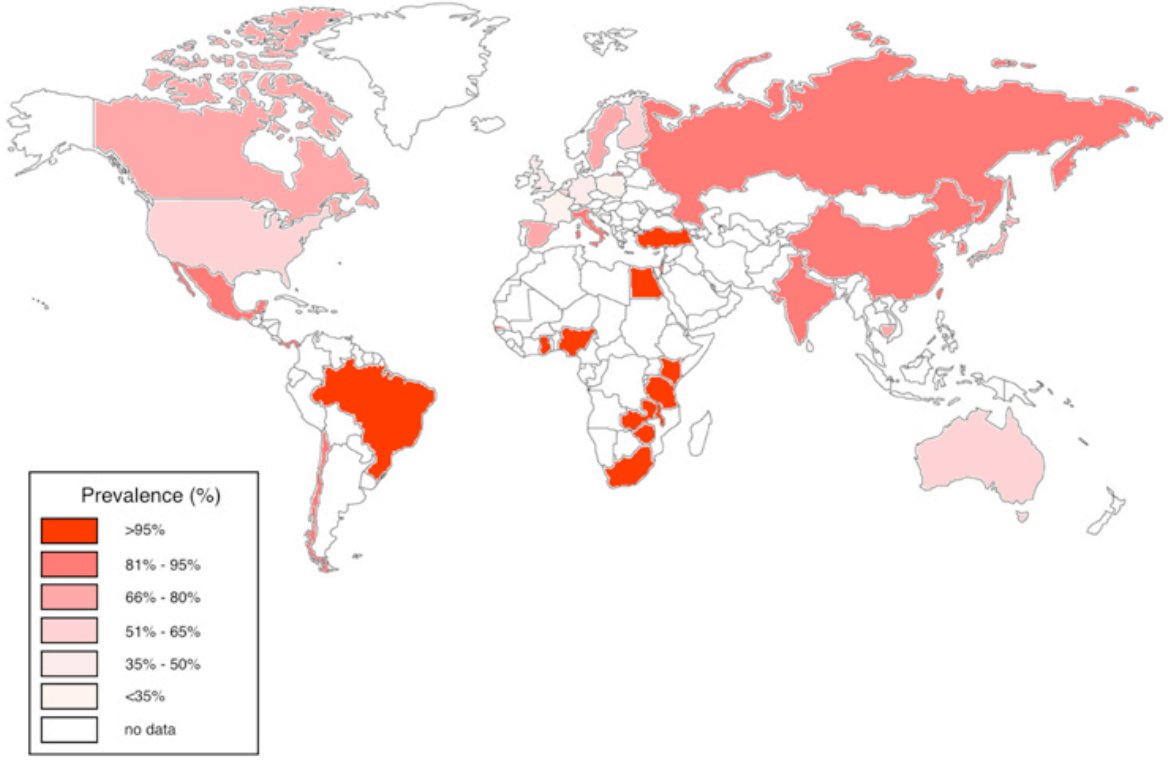
Fetal infection

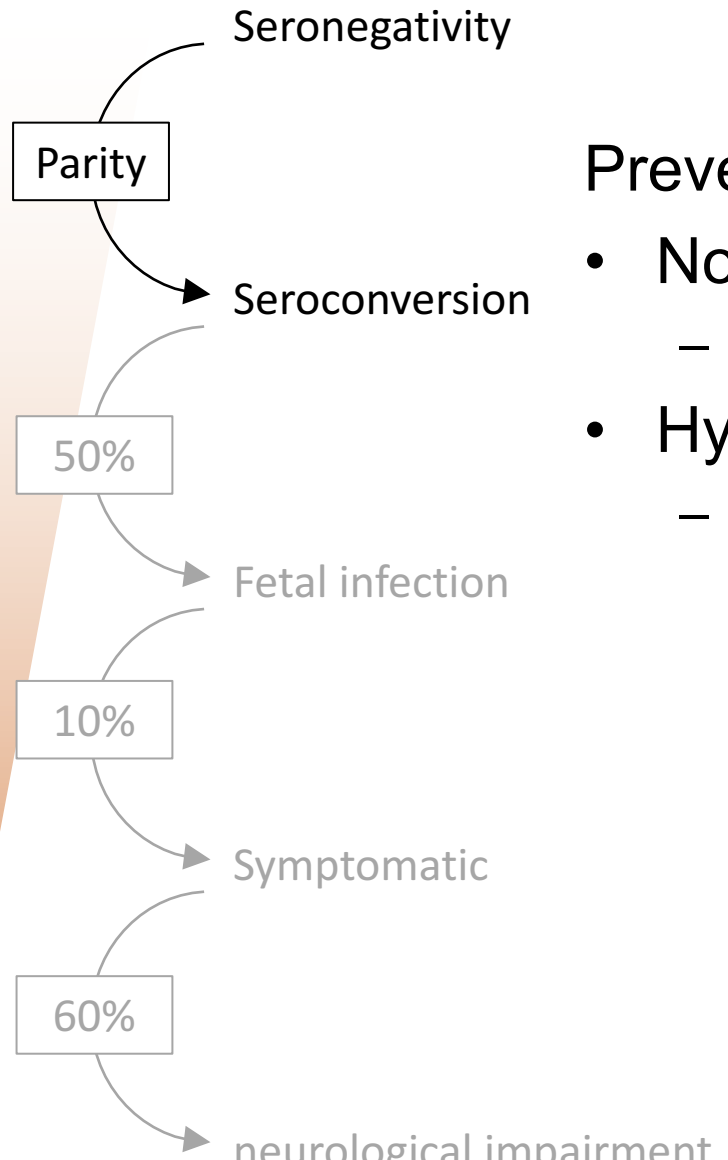
10%

Symptomatic

60%

neurological impairment

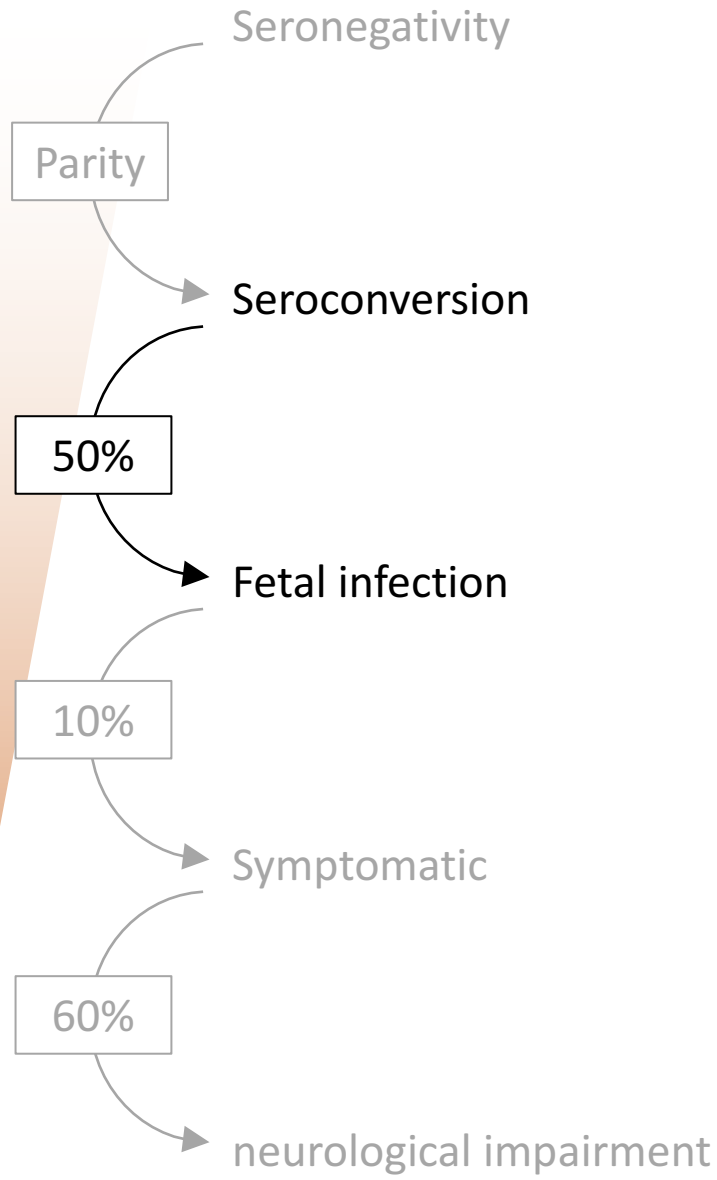




Prevention of seroconversion:

- No vaccine available
  - Best overall efficacy was 50% [1]
- Hygiene and behavioural interventions
  - Logical but uncertain efficacy on seroconversion rate [2,3]

[1] Pass RF, N Engl J of Medicine, 2009, 360: 1191-99,
[2] Adler et al, J Pediatrics, 2004, 145: 485-91,
[3] Vauloup-Fellous C, J Clin Virol, 2009, 46: S49-S53



Secondary prophylaxis by Hyperimmune globulin prophylaxis

- One exploratory study: Risk reduction / fetal infection of 24%[1]
- One randomized, double-blinded, placebo controlled study: NS risk reduction[2]
- One ongoing trial in the US, adequately sized[3]

[1] Nigro G, N Engl J of Medicine, 2005, 353: 1350-1362,
[2] Revello MG, N Engl J of Medicine, 2014, 370: 1316-26
[3] NCT01376778

Seronegativity

Parity

Seroconversion

50%

Fetal infection

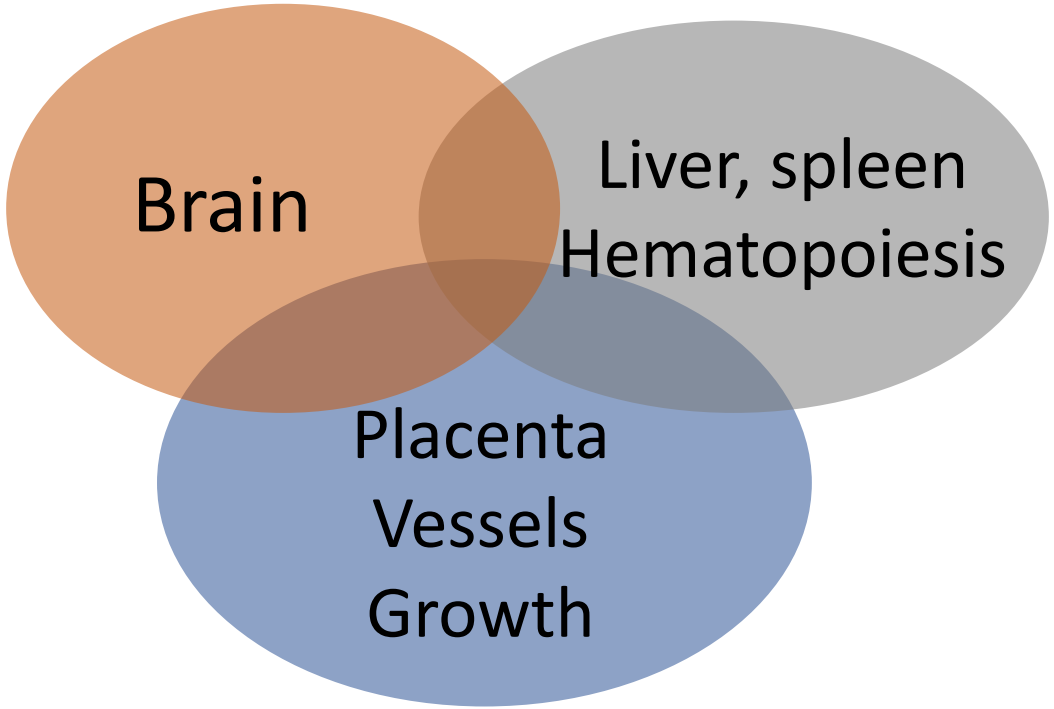
10%

Symptomatic

60%

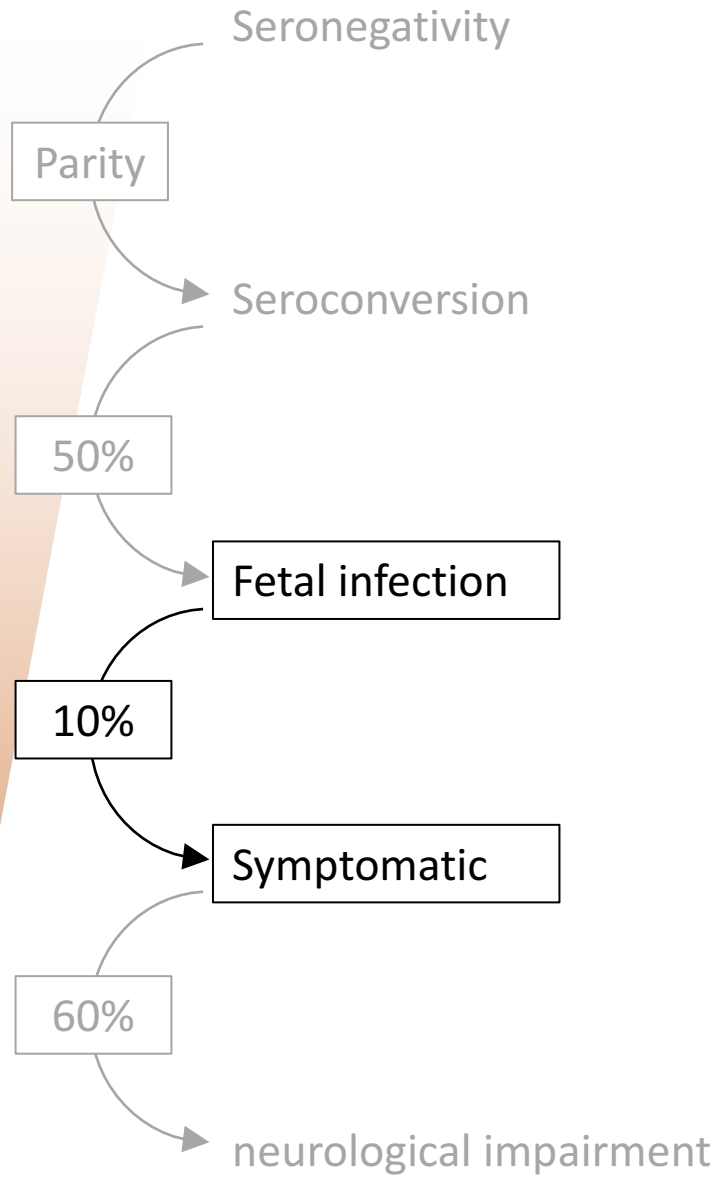
neurological impairment

Multisystemic disease



Full prognostic assessment

- Ultrasound
- Amniocentesis
- Fetal blood sampling
- MRI



Extracranial imaging

Placentitis
Oligohydramnios / *Polyhydramnios*
Hyperechoic bowel
Meconial peritonitis /Ascites
Liver & Spleen enlargement
Ubiquitous Calcifications
Pericardial / Pleural Effusion
Dilated Myocarditis
Heart Calcifications
Hydrops

Growth Restriction / Small for GA

Seronegativity

Parity

Seroconversion

50%

Fetal infection

10%

Symptomatic

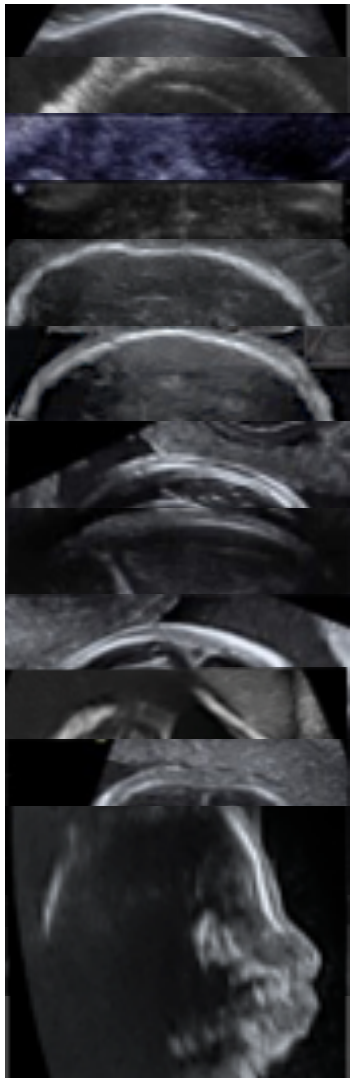
60%

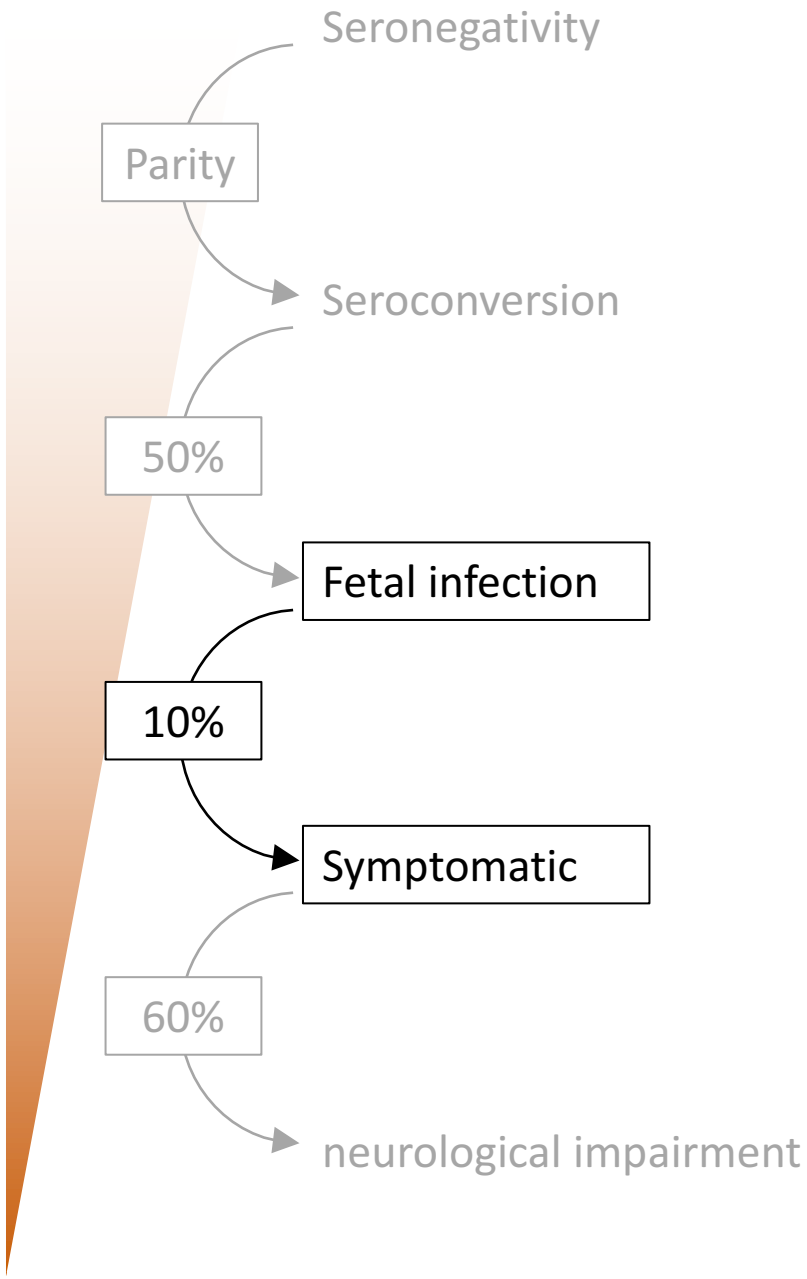
neurological impairment

Intracranial symptoms imaging

Ventriculomegaly
Parenchymal calcifications
Sub-ependymal Cysts
Calcifications of lenticulostriate v.
Intraventricular septation

Periventricular Hyperechogenicity
Periventricular cysts
Cystic Periventricular leukomalacia
Abnormal Gyration / Lissencephaly
Polymicrogyria
Microencephaly
Microcephaly





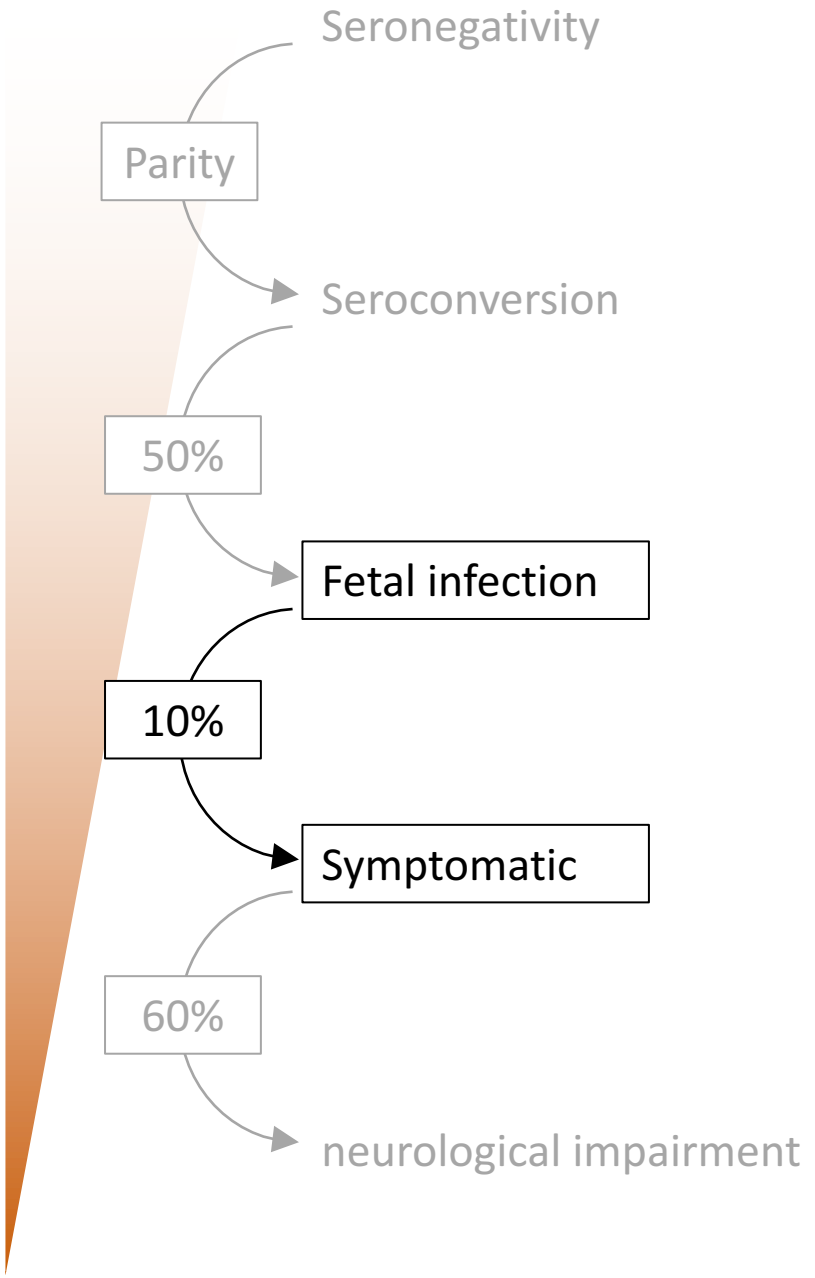
Symptomatic at birth

Fowler 1992

- Petechiae
- IUGR
- Hepato-splenomegaly
- Microcephaly
- Jaundice

Revised definition

- Petechiae
- IUGR
- Hepato-splenomegaly
- Microcephaly
- Jaundice
- Auditory tests
- Platelets/liver tests
- Transcranial US



Symptomatic at birth

AF PCR+, 20-28 wks
N=82

Severe brain
N=19

Non-severe US anomalies
N=22

Intracranial anomalies
Intraventricular adhesions
Lenticulostriate vascuolpathy
Subependymal cysts
Calcifications
Extracranial anomalies
Hepatosplenomegaly
Placentomegaly
IUGR
Hyperechoic bowel
Edema

TOP (severe) n=3
Symptomatic n=11
Asymptomatic n=8

Symptomatic n=9
Asymptomatic n=10

Symptomatic n=0
Asymptomatic n=38

Leruez-Ville, AJOG 2016

Seronegativity

Parity

Seroconversion

50%

Fetal infection

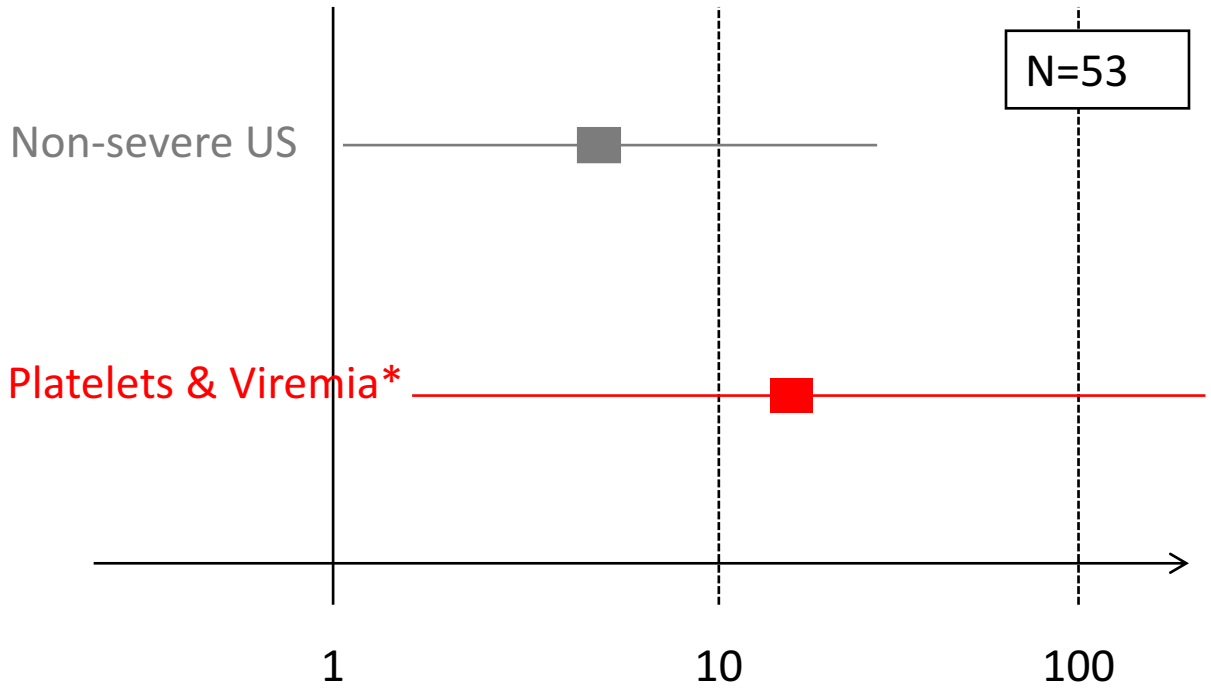
10%

Symptomatic

60%

neurological impairment

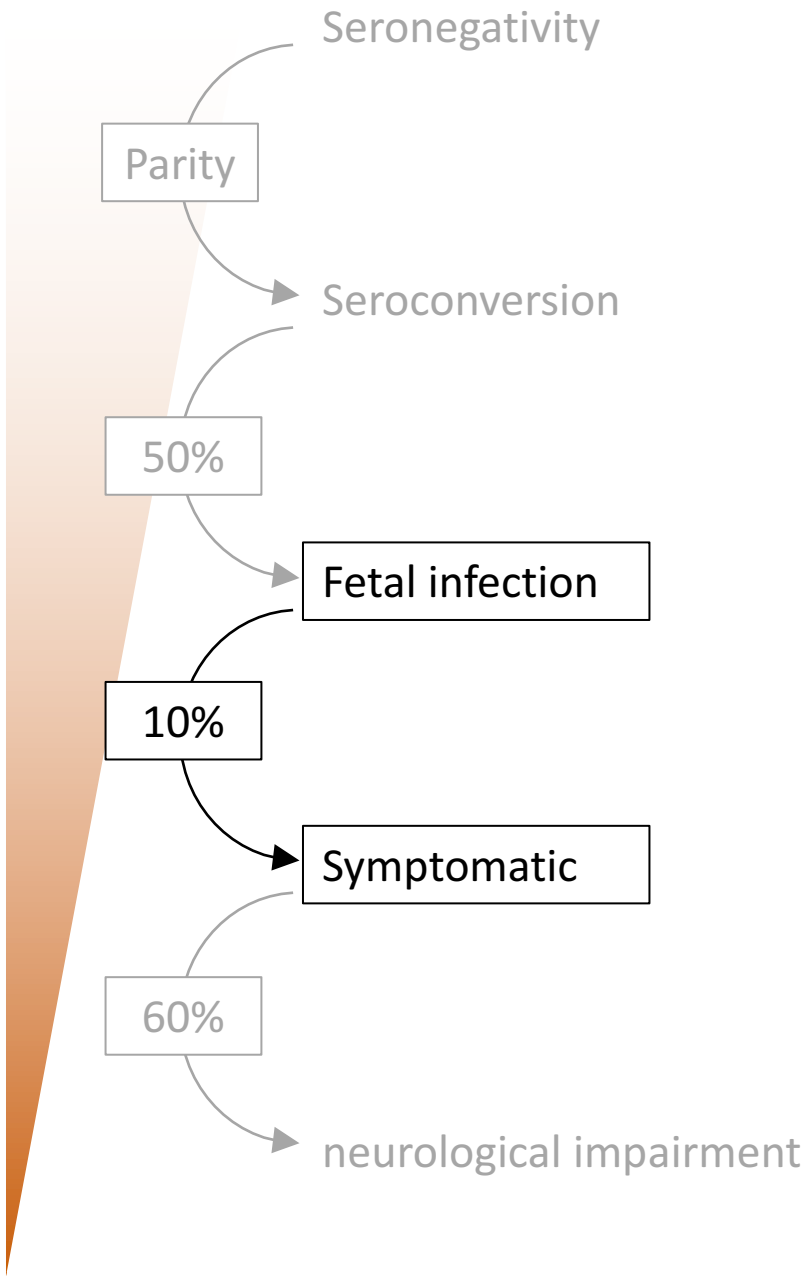
Symptomatic at birth
Midtrimester assessment



Ultrasound and biology are independant predictors

PPV = 50% NPV = 100%

*viral load > 5 log or platelets < 115000/mm3 Leruez-Ville, AJOG 2016



Who should we treat?

Mid-trimester assessment
AF PCR+

No US anomalies
No FBS anomalies*

Non-severe US anomalies

No US anomalies
FBS anomalies*

Severe brain
N=19

* High viral load or low platelets

Leruez-Ville, AJOG 2016

CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

In vitro: ValACV is **not** the most efficient drug against CMV

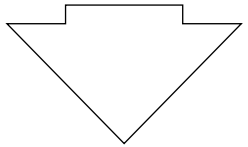
But

Clinical efficacy: **high** valACV dosage **(2gx4/day)** has proved efficient to prevent CMV disease in transplanted patients [Lowance et al,N Engl J Med 1999].

PK/PD [Jacquemard, BJOG 2009]:
Good placental passage, therapeutic fetal concentrations
Possible impact on viral load and platelets in infected fetuses

Best safety profile:
No cell transformation, no increase risk of neoplasia in vitro
No association with an increased risk of birth defects in thousand of women exposed in pregnancy [Stone et al, 2004; Pasternak, JAMA, 2010]

Good maternal tolerance



ValACV 2g x 4 / day for > 6 weeks

NCT01651585 AJOG 2016

CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

INCLUSION

Extra-cerebral anomalies

Intrauterine growth restriction (IUGR)
Abnormal amniotic fluid volume
Ascites and/or pleural effusion
Skin edema
Hydrops
Placentomegaly > 40 mm
Hyperechogenic bowel
Hepatomegaly > 40 mm
Splenomegaly > 30 mm
Liver calcifications

Non-severe cerebral anomalies

Moderate ventriculomegaly (<15 mm)
Isolated cerebral calcifications
Isolated intraventricular adhesion
Calcifications of lenticulate vessels

Biological anomalies

Fetal viremia > 3000 copies/ml
Fetal platelets < 100 000/mm3

EXCLUSION

Severe cerebral anomalies

Ventriculomegaly ≥ 15mm
Hydrocephalus
Microcephaly (HC<3SD)
Megacysterna magna >10 mm
Vermian hypoplasia
Porencephaly
Lissencephaly
Abnormal corpus callosum

Contra-indication to ValACV

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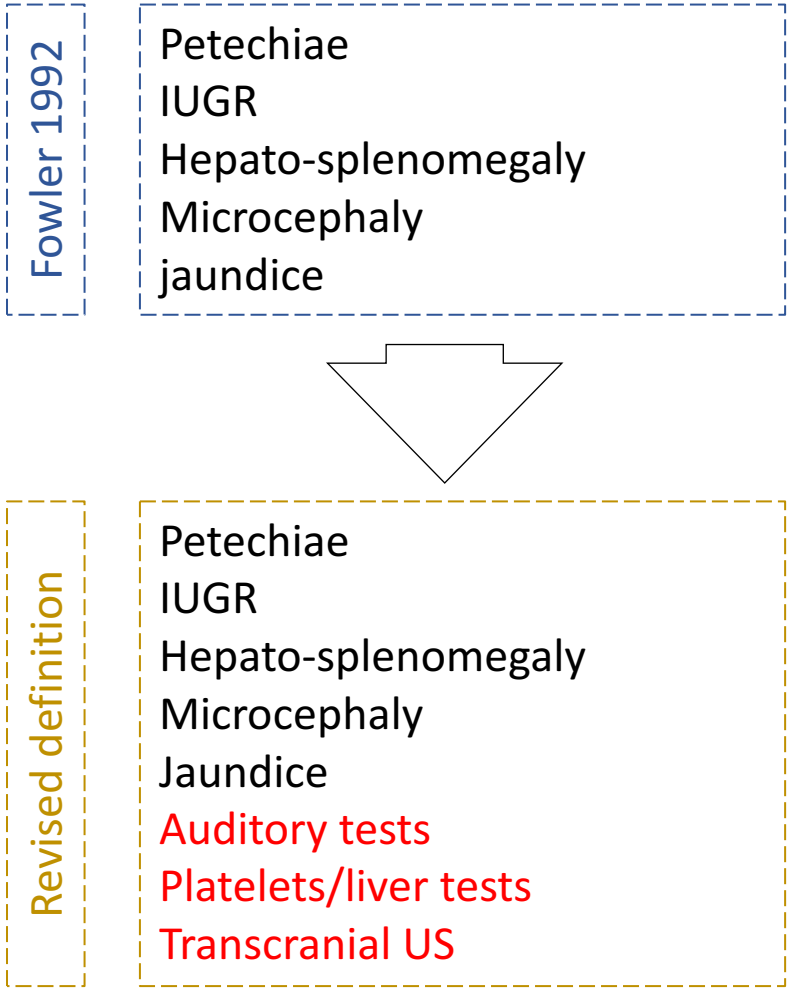
CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

Primary outcome: symptomatic at birth



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CYMEVAL 2

Failure of CYMEVAL 1

Double-blinded placebo-controlled RCT

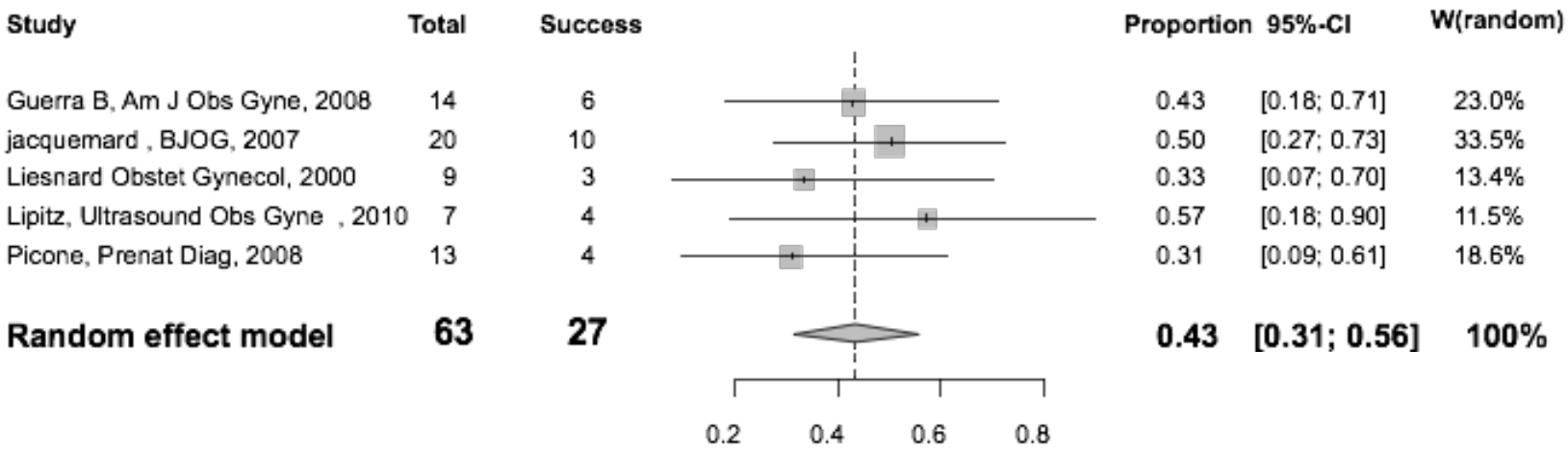
ValACV vs. placebo in moderately symptomatic infected fetuses

Failed because women refused the possibility of placebo

CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

Phase 2 design: to test the effect of ValACV against a plausible estimate



P0 = non acceptable proportion of asymptomatic infants < 60%

P1 = acceptable proportion of asymptomatic infants ≥ 80%

2-step Simon design (α=5%, Power=80%):

First step: 11 cases

If at least 7 / asymptomatic, continue up to 43 cases

NCT01651585 AJOG 2016

CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

Characteristics	Median [Interquartile range] or (%)
Women (N=41)	
Parity ≥ 1	30 (73.2)
Gestational age at primary infection (wks)	10 [7.8–16.2]
Gestational age at inclusion (wks)	25.9 [24.1–31.7]
Interval between primary infection and inclusion (wks)	16 [12.3–18.6]
Fetuses (N=43)	
Fetal blood CMV DNA load > 3000 copies/mL	3 (7)
Fetal growth restriction no. (%)	3 (7)
Abnormal amount of amniotic fluid no. (%)	3 (7)
Ascites and/or pleural effusion no. (%)	1 (2.3)
Placentomegaly no. (%)	13 (30.2)
Hyperechogenic bowel n (%)	25 (58.1)
Hepatomegaly no. (%)	6 (14)
Splenomegaly no. (%)	9 (20.9)
Liver calcification no. (%)	1 (2.3)
Moderate cerebral abnormality n (%)	5 (11.6)

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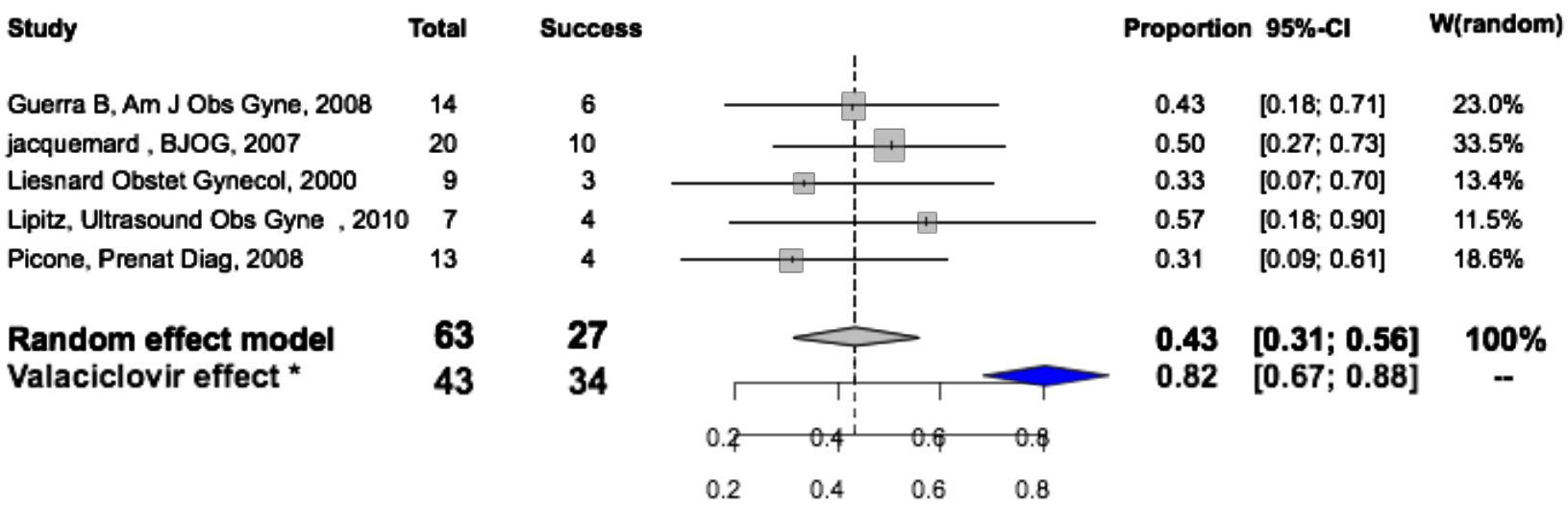
CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

	First Step	Second Step
Outcome		
Asymptomatic neonates	8	34
Symptomatic neonates or TOP	3	9
Total	11	43



ValACV is a potential effective therapy in moderately symptomatic fetuses

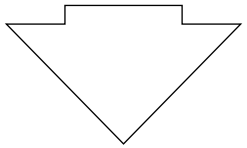
NCT01651585 AJOG 2016

CYMEVAL 2

Phase 2: Valacyclovir for the infected fetus

Cymeval 2: limitations

1. ValACV is not the best antiviral drug
2. Non-randomized
3. Over-estimation of severity?



Cymeval 3

Randomize ValACV vs ValGanciclovir

Fetuses with at least 2 symptoms