National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

# **The CROCUS-study -** Disease burden of congenital CMV infection in the Netherlands

Marjolein Korndewal

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CMV Public Health &
Policy Conference

LUMC
Leiden University Medical Center

CROCUS

National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

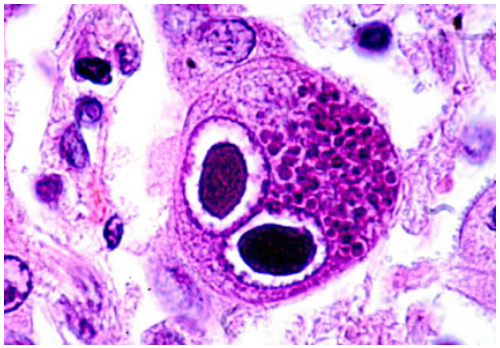
Centre for Infectious Diseases, Epidemiology and Surveillance
Centre for Infectious Disease Research, Diagnostics and Screening

LUMC
LEIDEN UNIVERSITY MEDICAL CENTER

Department of Medical Microbiology
Willem-Alexander Children's Hospital

# Congenital CMV infection

Cytomegalovirus



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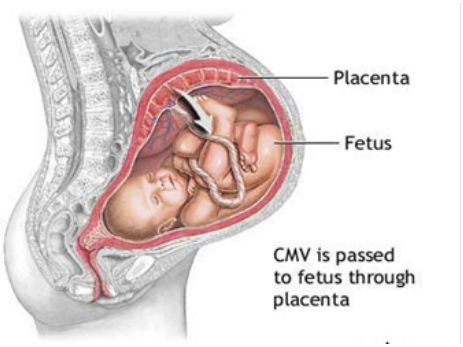
Congenital CMV-infection

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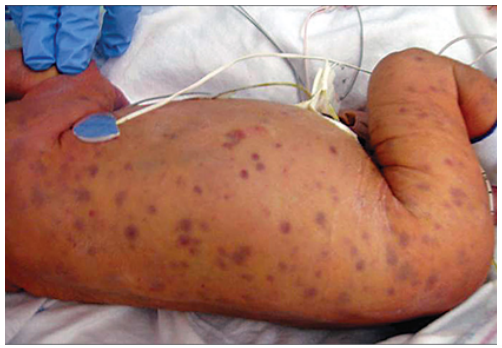
Symptoms at birth



Long term sequelae

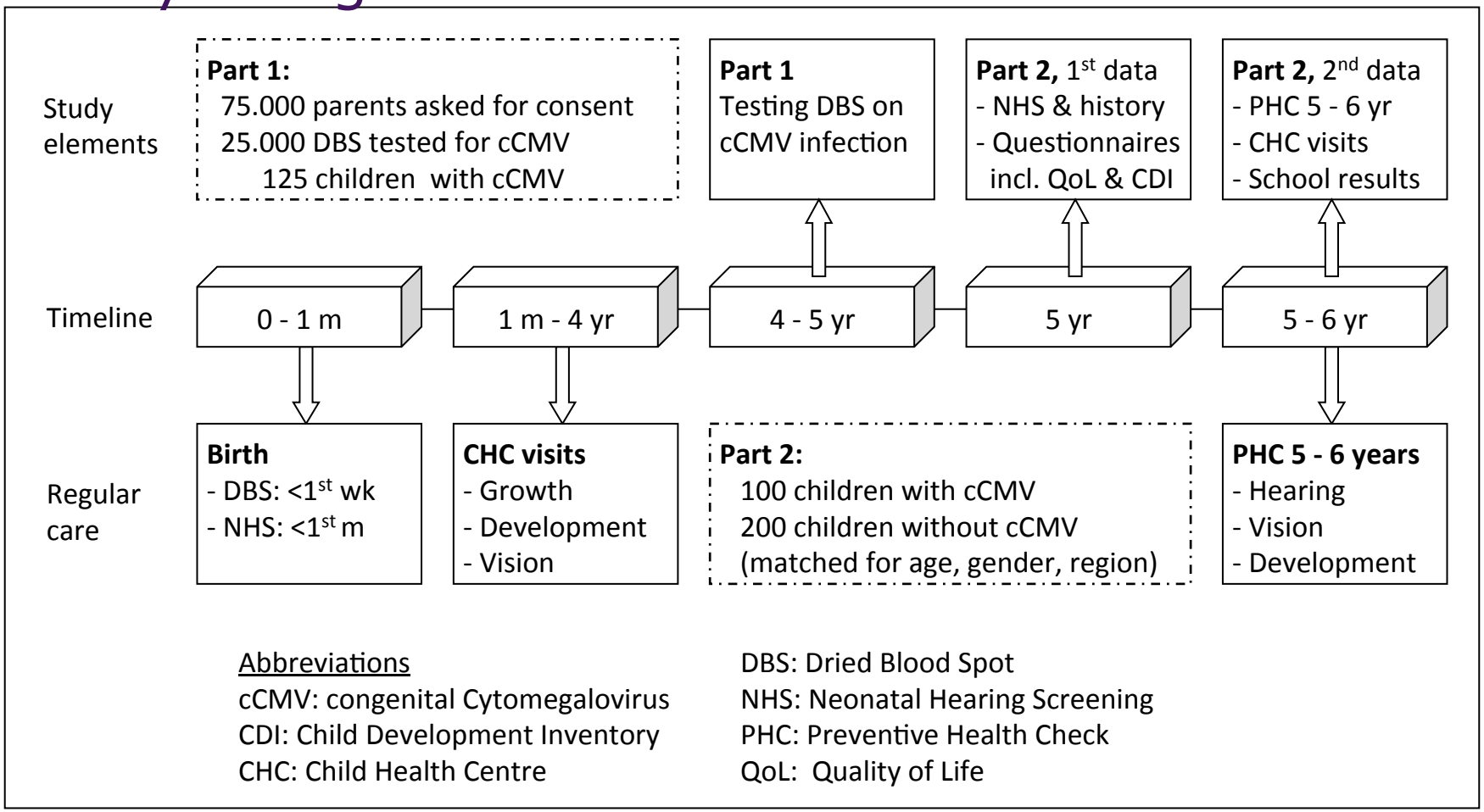
1 : 8

# CROCUS-study

- Objective
  - Long term sequelae of congenital CMV infection in Dutch children
    - Sensorineural hearing loss (5-6 years)
    - Cognitive, motor and visual impairment (0-4 years)

- Implications
  - Preventive measures
    - Primary prevention (vaccination)
    - Secondary prevention (neonatal screening)

# Study-design




Abbreviations

cCMV: congenital Cytomegalovirus
CDI: Child Development Inventory
CHC: Child Health Centre
DBS: Dried Blood Spot
NHS: Neonatal Hearing Screening
PHC: Preventive Health Check
QoL: Quality of Life

# Study design - Outcome

| Outcome | CHC (0-4 yr) | PHC (5-6 yr) | Other |
|---|---|---|---|
| Hearing function | Neonatal Hearing Screening | Screening Audiogram | Audiological center |
| Visual function | VOV / APK | Landolt C | Ophthalmologist |
| Cognitive function | Van Wiechen | - | CDI<br>School results |
| Motor function | Van Wiechen | Baecke Fassaert Motor Test | - |
| Quality of Life | - | - | SF-12<br>PedsQL |
| Clinical history | - | - | Family physician<br>Pediatrician |
| Growth | Growth Chart | Length, Weight | |

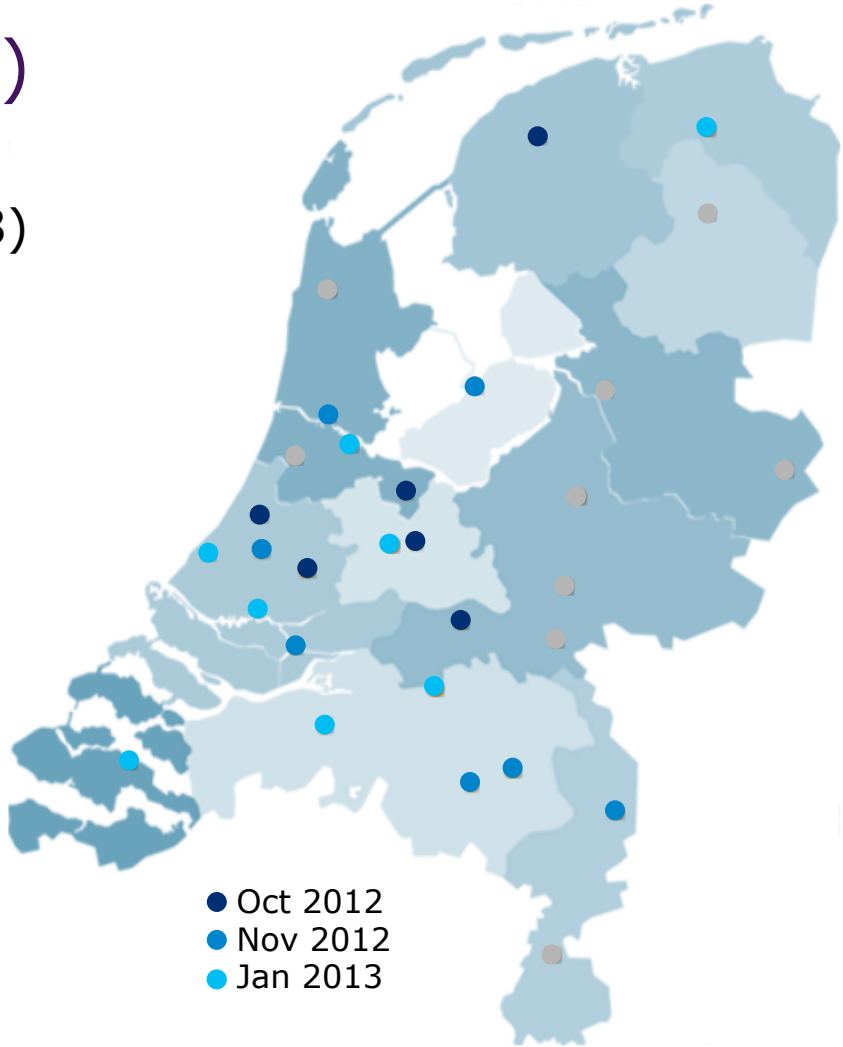
# Study design – Diagnosis

- Diagnosis of congenital CMV infection:
  - PCR on CMV DNA in dried blood spot (DBS)
  - Screening of DBS (RIVM)
    - 2 targets (UL55 and UL123)
  - Confirmation of diagnosis (LUMC)
    - triplo-test (UL 123)

# Results – Response (part 1)

- **Municipal Health Services** (n = 28)
  - 19 participation
  - 4 no participation
  - 5 no response

- **Parents** (n = 73.693)
  - Response: 34.088 (46.3%)
    - Yes: 32.469 (97.5%)
    - No: 825 (2.5%)



# Results – DBS testing (part 1)

- Testing of DBS on CMV DNA
  - Tested 31.583 DBS
  - Confirmed 160 DBS CMV+

- CMV infection in DBS: 160 children
  - - 6 children: DBS > 21 days after birth
  - +2 children: prior diagnosis (no material left)

- **Congenital CMV infections**: 156 children
  - **0.49% (95% CI: 0.41-0.56)**

# Results – Part 2 – Preliminary data!

| **Symptoms (CMV positive, n = 156)** | Number | Percentage |
|---|---|---|
| **Related cCMV-infection** | **10** | **6,4%** |
| Severe neurologic disorder | 2 | 1,3% |
| Severe developmental delay | 8 | 5,1% |
| Perceptive hearing loss | 3 | 1,9% |
| **Probably related to cCMV-infection** | **9** | **5,8%** |
| Developmental delay - multiple areas | 9 | 5,8% |
| **Possibly related to cCMV-infection** | **24** | **15,4%** |
| Developmental delay – mild / single area | 13 | 8,3% |
| Premature / icterus | 12 | 7,7% |
| **Not related to cCMV-infection** | **29** | **18,6%** |
| Ear problems (T-tubes/ ear-infections) | 26 | 16,7% |

# Results – Part 2 – CMV positive

- Children with **known congenital CMV infection** (n = 4)

  - 2 diagnosed within first year, long term sequelae
    - Cerebral palsy and hearing loss
    - General developmental delay
  - 1 diagnosed at birth, treated with valganciclovir, no sequelae
  - 1 diagnosed after first year, hearing loss

# Results – Part 2 – CMV positive

- Children with **unknown congenital CMV infection** and **symptoms related** to congenital CMV infection (n = 7)
  - 1 Polymicrogyria, severe developmental delay, epilepsy
  - 1 Sudden onset hearing loss at age of 5 years
  - 1 General developmental delay and hearing loss
  - 3 General developmental delay and (suspected) autism
  - 1 General developmental delay

- Children with **unknown congenital CMV infection** and **symptoms probably related** to congenital CMV infection (n = 9)
  - Developmental delay at multiple areas

# Results – Part 2 – CMV positive (n = 156)

- Neurological problems
  - 1 (0.6%) Polymicrogyria, epilepsie
  - 1 (0.6%) Cerebral palsy (known cCMV)

- Cognitive development
  - 9 (5.8%) Developmental delay
  - 4 (2.6%) Mild developmental delay

- **Motor development**
  - 16 (10.3%) Developmental delay
  - 7 (4.5%) Clumsy

# Results – Part 2 – CMV positive (n = 156)

- **Hearing loss**
  - 6 (3.8%) hearing loss (1 osteogenesis imperfecta, 1 middle ear bones problems)
  - 26 (16.7%) ear problems (tympanostomy tubes, ear infections)

- Speech – language development
  - 12 (7.7%) language and speech developmental delayed
  - 6 (3.8%) speech problem

- **Behavioral development**
  - 4 (2.6%) autism / PDD-NOS
  - 2 (1.3%) behavioral problem / suspected for autism

# Implications

- **Overall**: 156 children CMV positive
  - 4 children with known congenital CMV infection (2.5%)

- **Children with symptoms related to cCMV** (n = 10)
  - 3 children: known congenital CMV infection (30%)
  - 7 children: unknown congenital CMV infection (70%)
    - polymicrogyria, severe development delay and epilepsy
    - late onset hearing loss (5 years of age)
    - 5 general developmental delay (and hearing loss / autism)

- **Children with symptoms probably related to cCMV** (n = 9)

**Underdiagnosis of congenital CMV infection**

# Conclusion

- Birth prevalence of congenital CMV infection:
  - 0.49% (0.41% - 0.56%)

- Symptoms (probably) related to congenital CMV infection:
  - 19 children with severe disorders (12.2%)

- Congenital CMV infection is underdiagnosed in the Netherlands
  - 3 / 19 children with symptoms (15%)

# Acknowledgement


National Institute for Public Health
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*Ministry of Health, Welfare and Sport*

LEIDEN UNIVERSITY MEDICAL CENTER

- Epidemiology & Surveillance
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# Questions or Suggestions

# Study design - Objective

- Prevalence of long term sequelae in Dutch children
  - Sensorineural hearing loss (5-6 years)
  - Cognitive, visual and motor impairment (0-4 years)
- Association between viral load and long term sequelae

# Study design - Implications

- Preventive measures
  - Primary prevention: Vaccination
    - Modelling
  - Secondary prevention: Neonatal screening
    - Early recognition and intervention
    - Potential treatment: anti-viral therapy

# Study design – Inclusion and Exclusion

- Inclusion criteria:
  - Participation in neonatal screening
  - Dried Blood Spot (DBS) stored for 5 years
  - Congenital CMV infection or Matched control

- Exclusion criteria:
  - No participation in neonatal screening
  - Dried Blood Spot (DBS) stored for 1 years
  - No informed consent
  - No visits to CHC or PHC

# Study design - Group size

- Power calculation:
  - 83 CMV positive children (10% SNHL)
  - 166 CMV negative children (0.1% SNHL)
- Inclusion:
  - 100 CMV + and 200 CMV –
- Screening:
  - 135 CMV + and 270 CMV –
- Testing:
  - 25.000 DBS
- Asking permission:
  - 50.000 – 75.000 parents

# Study design - Outcome (1)

- Hearing function
  - Screening youth health care (YHC)

    Screening audiogram

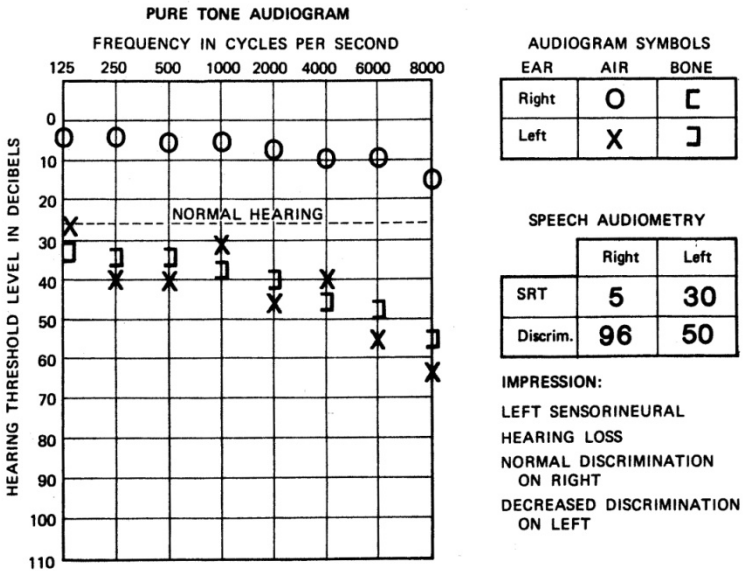
    → Audiological center

    › Sensitivity: 92%,

    › Specificity: 94%

  - Screening CHC:

    Neonatal Hearing Screening




 van Leerdam 1998 (YHC), van der Ploeg 2009 (TNO) 

# Study design - Outcome (2)

- Visual function
  - Screening YHC:

    Landolt-C

    → Pediatric ophthalmologist

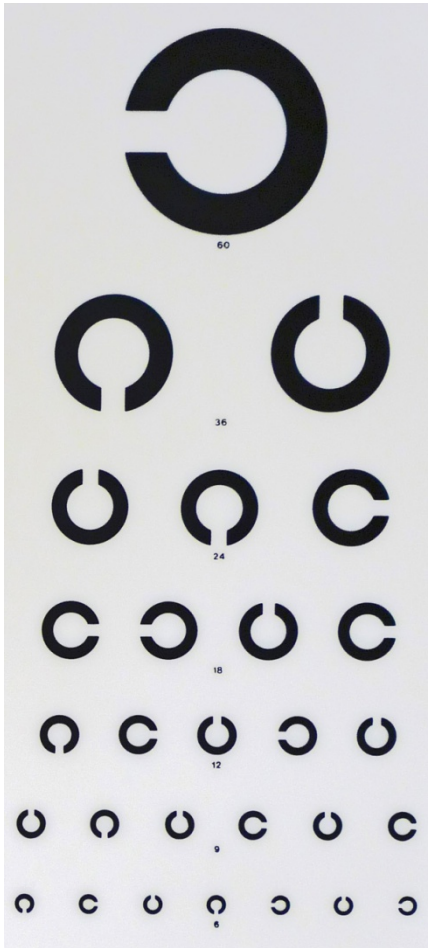
    › Sensitivity / Specificity:

    not known (reference test)

  - Screening CHC:

    VOV (‘vroege opsporing visusafwijking’)

    APK (‘amsterdamse plaatjes kaart’)



# Study design - Outcome (3)

- Cognitive function
  - Child Development Inventory (CDI)

    Parent questionnaire on child development

    › Sensitivity: 73-87% (15-72 months),

    › Specificity: 86-96%

  - School results: 'Leerlingvolgsysteem' (LVS)

    › Ordening: Accuracy of Measurement (MAcc): 0.84-0.89

    › Language for toddlers: MAcc: 0.82-0.84

    › Space and Time: Macc: 0.81-0.86


Doig 1999, Duyme 2011, Rydz 2006, Lansink 2010, van Kuijk 2001

# Study design - Outcome (4)

- Motor function
  - Screening YHC:

    Baecke Fassaert Motor Test (BFMT): often incomplete

    › Sensitivity / Specificity: not known

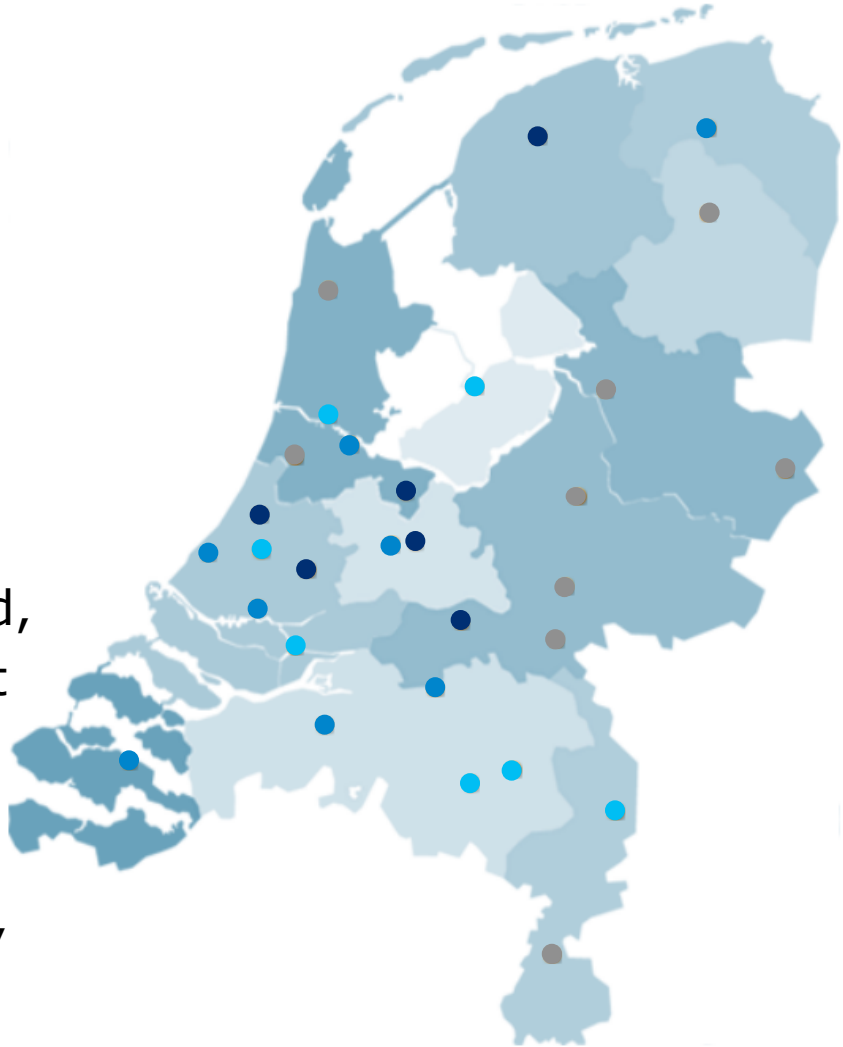
  - Screening CHC:

    Van Wiechen Development Test

    › Sensitivity / Specificity: not known

# Municipal Health Services

- **1st mailing** (Oct. 2012)
  Fryslan, Gooi en Vechtstreek,
  Hollands Midden, Midden-Nederland,
  Rivierenland
- **2nd mailing** (Nov. 2012)
  Zuid-Holland Zuid, Zaanstreek-
  Waterland, Flevoland, Limburg Noord,
  Brabant Zuidoost, Zuid-Holland West
- **3rd mailing** (Jan. 2013)
  Utrecht, Zeeland, Den Haag,
  Groningen, Rijnmond, West-Brabant,
  Hart van Brabant, Amsterdam



# Limitations

- Participation bias
  - Different response rates for children with health problems
    → Possible over- or underrepresentation
    › 8% of children with hearing loss have congenital CMV infection
    → Overrepresentation of these children in control group?
    › 4% of children with symptomatic congenital CMV infection die before the age of 5 years

- Information bias
  - Data collection after diagnosis
    → Parental questionnaires (QoL)
    → YHC-physician (observer bias)

# Limitations

- Diagnostic test
  - PCR for CMV in dried blood spots
    - Specificity: > 99%
    - Sensitivity: depends on viral load (50-100%)

- Data collection
  - Data collection by Youth Health Centre (YHC)
    - Difference in registration (per region / per physician)

    → Use of most objective outcome measures (e.g. audiogram)

- Confounding (differs per outcome measure)
  - Possible confounders: socio-economic status, ethnicity
  - Other covariates: breast feeding, prematurity, clinical history

# DBS testing – Problems

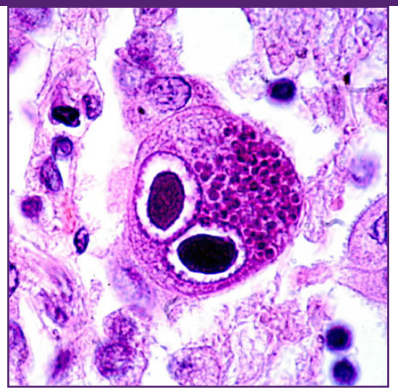
- Difference LUMC - RIVM
  - Contamination (at first – solved later on)
  - Viral load around detection limit
  - Lower sensitivity with lower viral load

- Missing DBS
  - Not enough material
  - DBS not available / not found
  - Used for other purpose

# Results – Part 2 (preliminary data)

- Pregnancy and neonatal problems
  - 8 icterus
  - 7 premature (including 2 dysmature)
  - 5 neonatal infection
  - 4 HELLP/(pre-)eclampsia

# Cytomegalovirus (CMV)

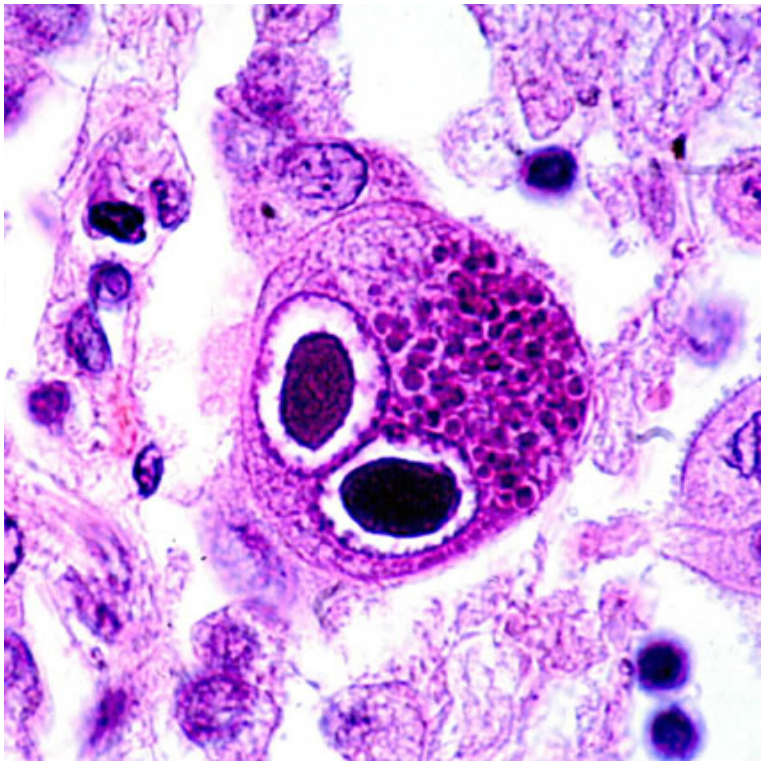


- Human cytomegalovirus
  β-herpes virus → life long latency
- Transmission
  Urine, saliva, placenta, breast milk, transplantation, sexual
- Healthy individuals
  Asymptomatic
- Immunocompromised
  Hepatitis, pneumonia, colitis, uveitis, encephalitis, myelitis
- Seroprevalence
  ~ 45% of Dutch population (PIENTER-2)

# Cytomegalovirus (CMV)

- Human Cytomegalovirus:
  - Double-stranded DNA virus
  - Herpes virus (HSV, VZV, EBV)

- Life long latency:
  - Primary infection
  - Recurrent infection
    - › Reactivation
    - › Re-infection



# CMV infection - Symptoms

- Healthy individuals:
  - Asymptomatic
  - Mononucleosis syndrome

- Immunocompromised individuals:
  HIV/AIDS, transplant patient, fetus
  - Pneumonia, hepatitis, colitis,
  - Uveitis, retinitis,
  - Encephalitis, myelitis, and neuropathy

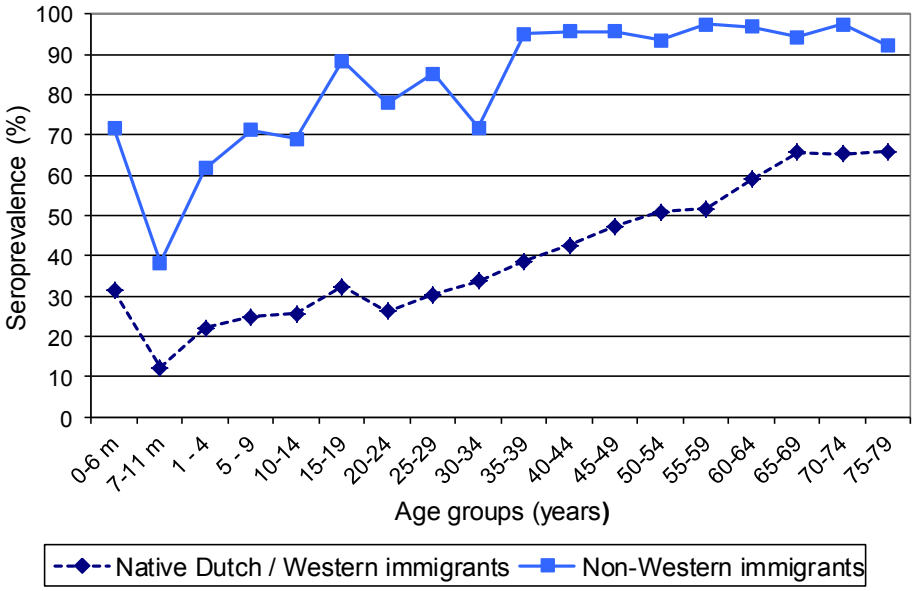
# CMV infection - Transmission

- Person to person
- Close contact with excreted virus (urine, saliva)

  - Placenta
  - Blood transfusions
  - Organ transplantation
  - Breast milk
  - Sexual transmission


# CMV infection - Prevalence

- CMV seroprevalence
  - The Netherlands: 49%
  - West - Europe / U.S.A.: 40-85%
  - Africa, South-America, Asia 95-100%



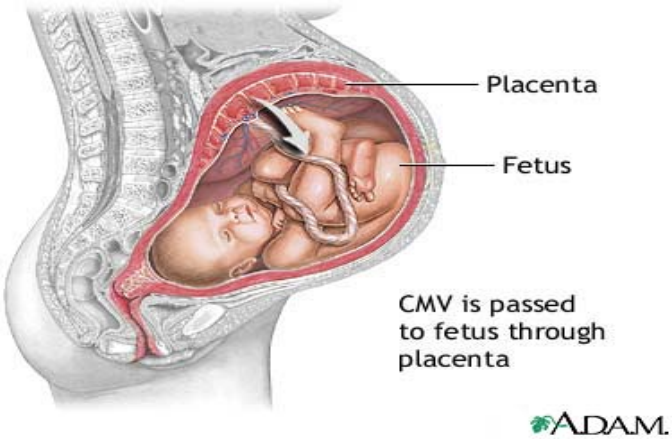

- Risk factors:
  - Socio economic status
  - (Non-Western) immigrants
  - Young children


PIENTER-2 unpublished results, Kenneson et al. 2007

# Congenital CMV infection

- Transmission from mother to fetus:
  - Primary maternal infection (32%)
  - Recurrent maternal infection (1.4%)

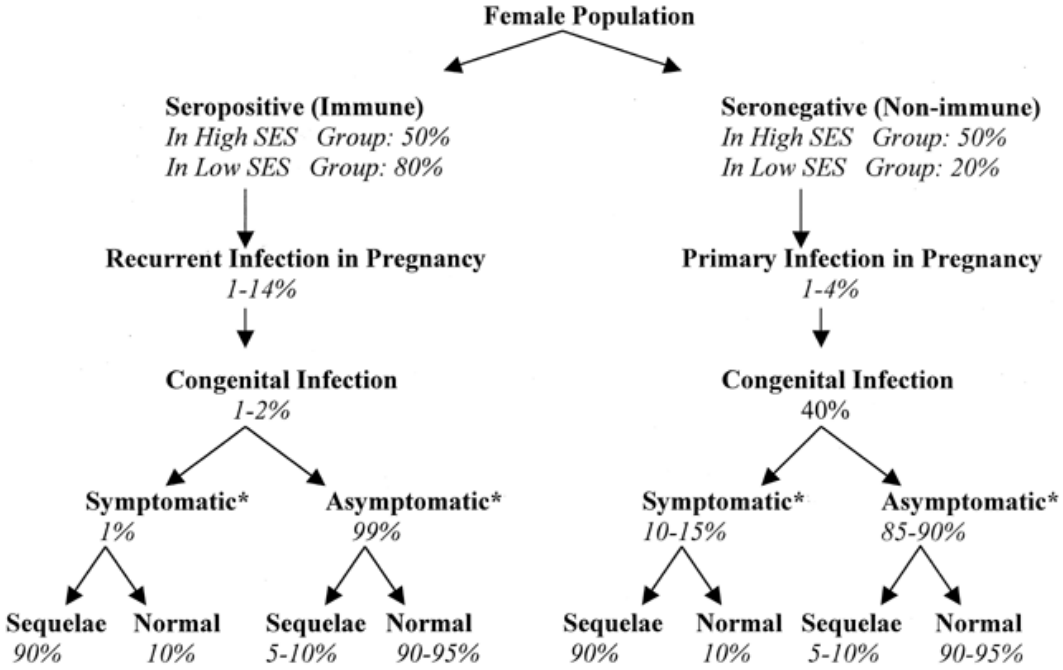
- Prevalence:
  - Worldwide: 0.6% - 0.7%
  - The Netherlands: 0.54%





Kenneson et al. 2007, De Vries et al. 2011

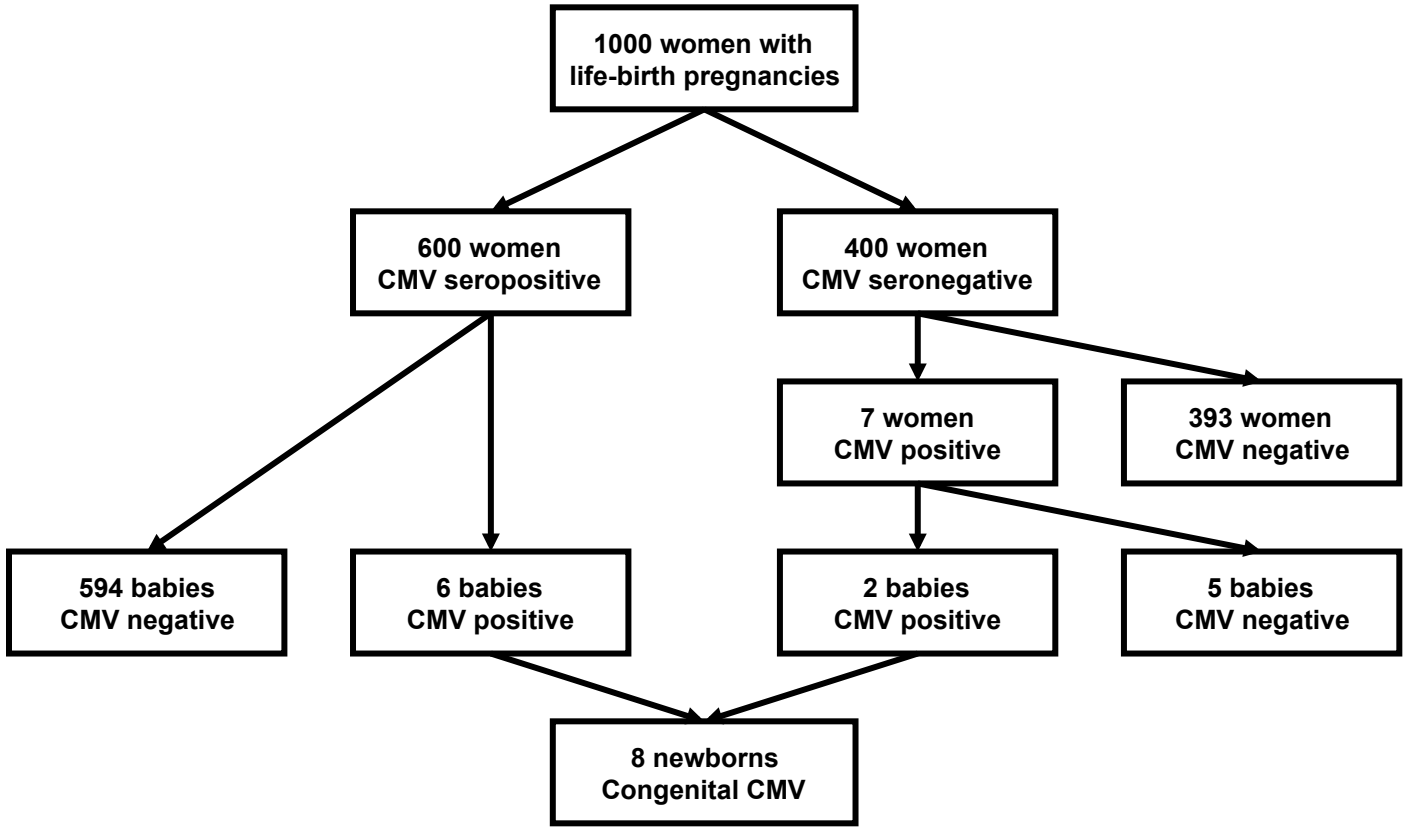
# Congenital CMV infection - Consequences




Primary infection → Symptomatic infection (10-15%)

Recurrent infection → Symptomatic infection (1%)

# Risk on congenital CMV infection

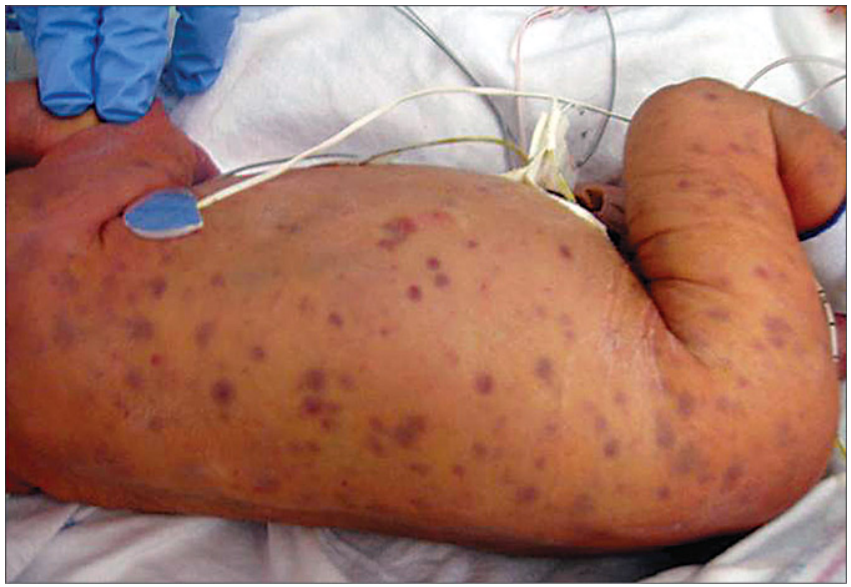




Cannon et al. 2009

# Congenital CMV infection - Symptoms

- Symptoms at birth: 12.7%
  - Hepatosplenomegaly
  - Jaundice
  - 'Blue-berry muffin rash'
  - Microcephaly
  - Intra-uterine growth retardation
  - Retinitis



- Asymptomatic: 87.3%

# Congenital CMV infection - Sequelae

- Long term sequelae
  - Sensorineural hearing loss (SNHL)
  - Development delay
    - Cognitive
    - Motor
  - Visual impairment

- Prevalence
  - Symptomatic: 40-58%
  - Asymptomatic: 13.5%

# Congenital CMV infection – Sequelae (2)

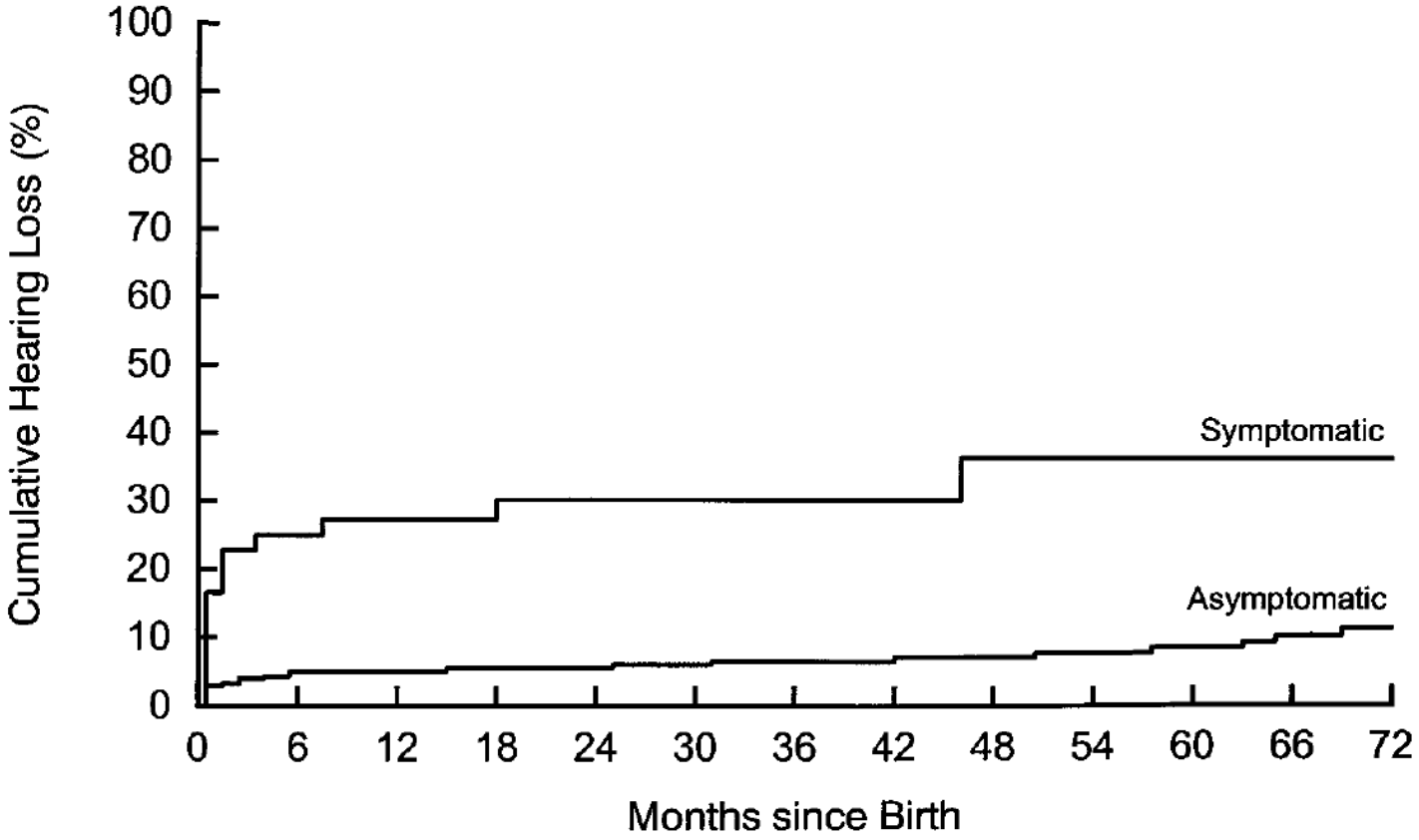
- Long term sequelae

| Long term sequelae | Symptomatic | Asymptomatic |
|---|---|---|
| Hearing impairment | 27-36% | 9.5-12% |
| Cognitive impairment | 66% | 6.5% |
| Visual impairment | 22% | 2.4% |
| Motor impairment | 6-9% | 0-5% |

- Association viral load and congenital CMV infection
  - Symptomatic (vs. asymptomatic): higher viral load
  - Hearing loss (vs. no hearing loss): higher viral load


Dollard 2007, Fowler 1992, Coats 2000, Lanari 2006, Boppana 2005, Rivera 2002

# Late-onset hearing loss




 Fowler et al. 1999

# Congenital CMV infection – primary vs. recurrent

- Prevalence symptomatic congenital CMV infection
  - Overall: 12.7%
  - Primary maternal infection: 10-15%
  - Recurrent maternal infection: 1%

- Prevalence long term sequelae
  - Symptomatic: 40-58%
  - Asymptomatic: 13.5%
  - Primary maternal infection: 25%
  - Recurrent maternal infection: 8%


Gardella 2008 (GLOWM), Fowler et al. 1992

# Long Term Sequalae