Human cytomegalovirus screening in pregnancy

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Introduction

Incidence of congenital cytomegalovirus infection in Ireland: Implications for screening and diagnosis

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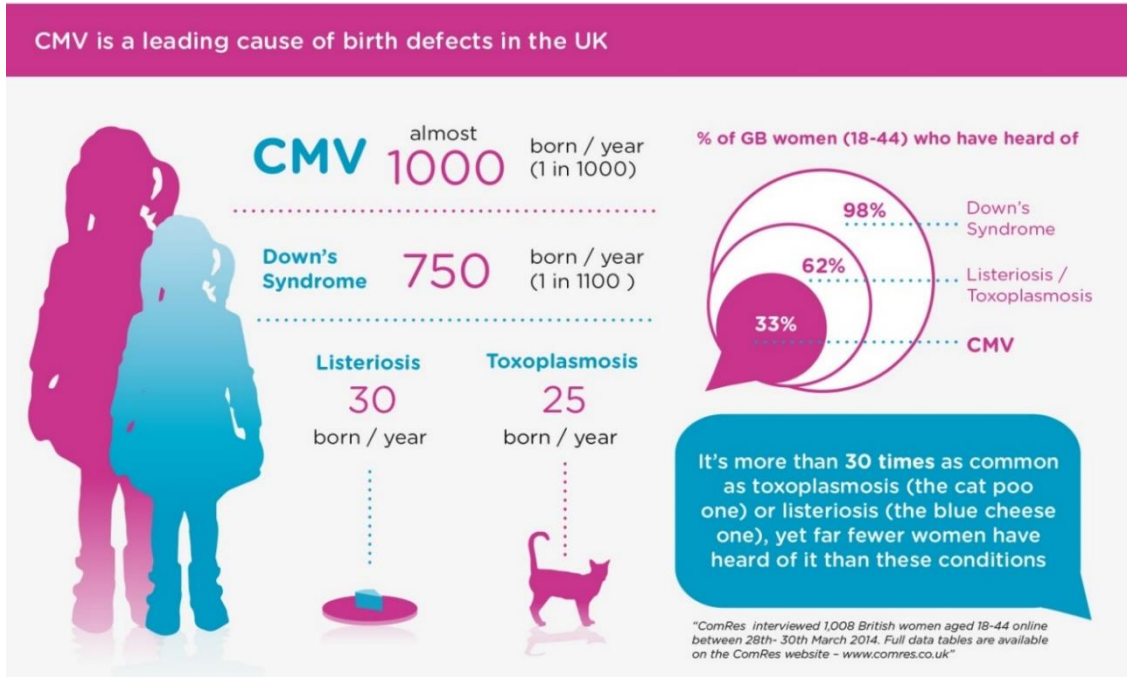
In the European Union - **37,800 cCMV-infected babies are born annually**, and 6807 (**18%**) will suffer **permanent clinical sequale**

- **10% of infected neonates are symptomatic at birth**
- The remaining **90% - asymptomatic** (approximately **15%** will **develop sequelae of CMV infection in the form of psychomotor impairment and SNHL**



http://cmvaction.org.uk/pregnant-women

In the absence of routine screening, asymptomatic infections during pregnancy (90% of all cCMV cases) - undiagnosed; many clinical abnormalities manifest later in childhood

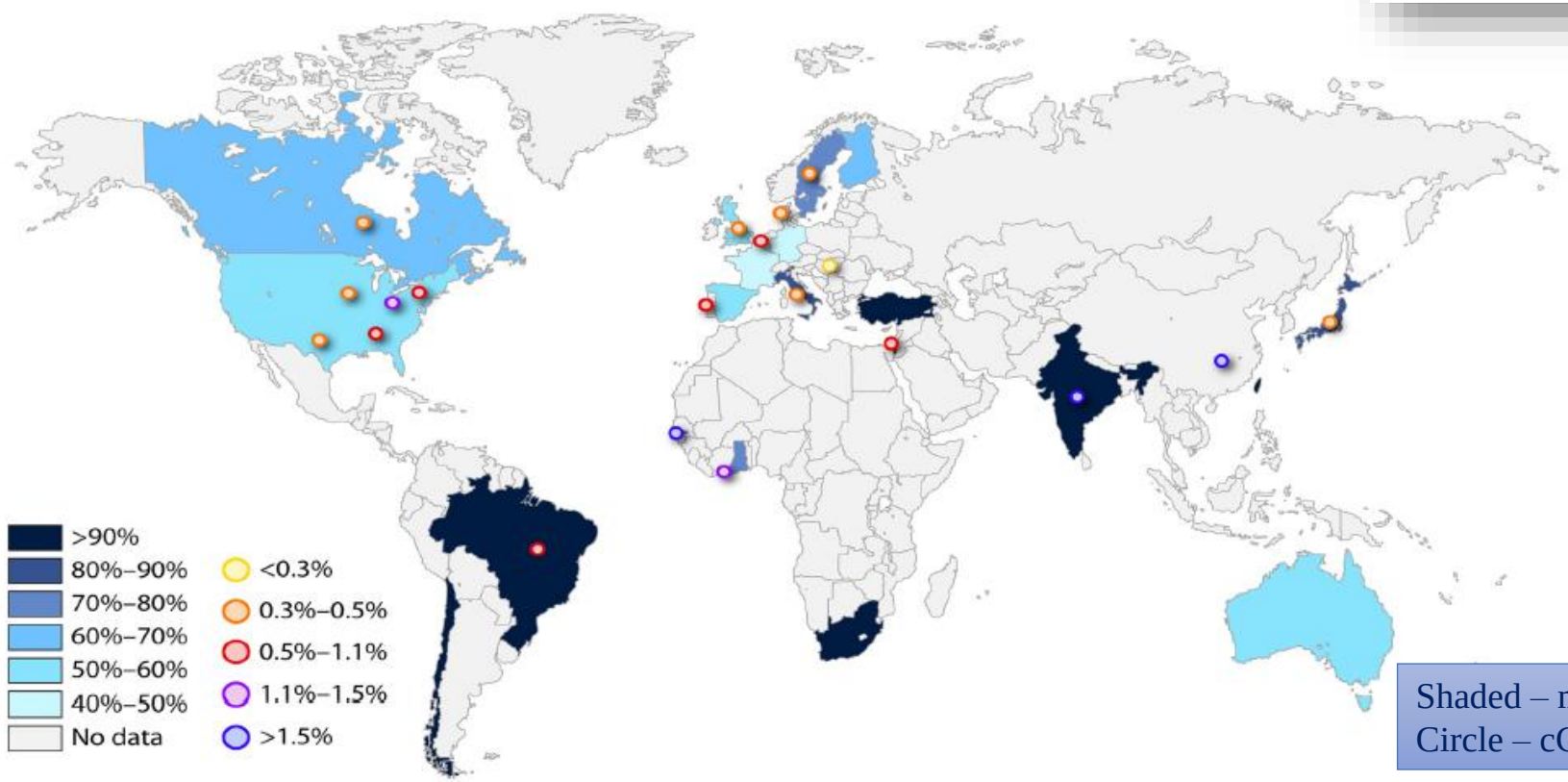
CMV seroprevalence during pregnancy

CMV aquisition – age-dependent rise in the seroprevalence
CMV seroprevalence during pregnancy 50-60%
Prevalence of cCMV infection 0.6-0.7%

CMR
Journals.ASM.org

The "Silent" Global Burden of Congenital Cytomegalovirus

Sheetal Manicklal,[a] Vincent C. Emery,[b] Tiziana Lazzarotto,[c] Suresh B. Boppana,[d] Ravindra K. Gupta[b]



Shaded – maternal seroprevalence
Circle – cCMV infection

Universal CMV serology during pregnancy

Antenatal CMV screening offered in a few countries: Israel, France, Belgium, Spain, Italy, Germany, Austria, Portugal, and The Netherlands – no official universal screening guideline – reason not to screen – the absence of medication to prevent transmission, the difficulty of predicting sequelae

Introduction of screening – several implications

Identify fetuses at risk of developing sequelae

Collect data about the maternal-fetal transmission

Development of laboratory diagnostics

Extensive education about the importance of hygiene measures during pregnancy

Laboratory diagnosis of CMV infection during pregnancy

Gold standard – to detect maternal seroconversion

- **Problems**
  - Initial specimen (IgM/IgG negative serum at the beginning of the infection) is rarely available
  - Anti-CMV IgM positive results – during reactivation or reinfection
  - Frequent false positive anti-CMV IgM – sensitivity of commercially available tests 30-88%
  - Positive anti-CMV IgM results – persisting up to 12 months after primary infection

Laboratory diagnosis of CMV infection during pregnancy

Perform - early in the first trimester (between 6 and 18 weeks of gestation)

Identify those who were **CMV-seronegative and provide hygiene counseling** to CMV-seronegative pregnant women - significantly prevents maternal infection

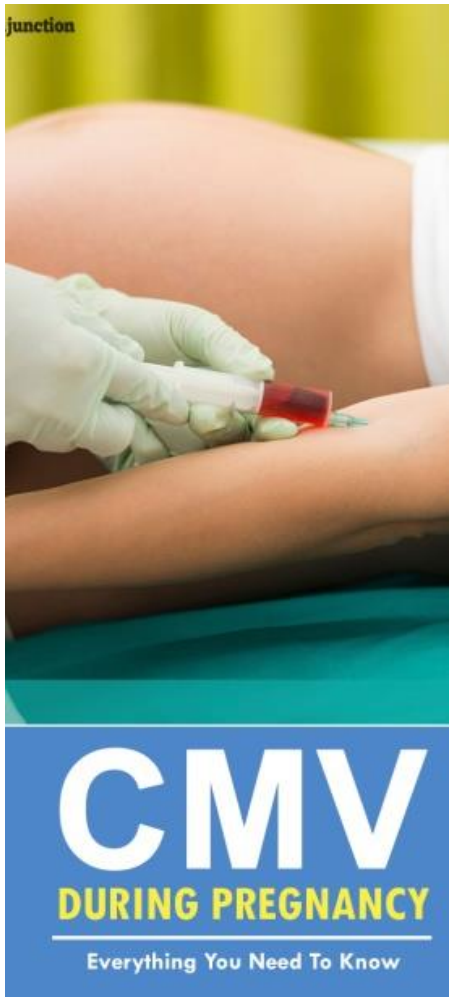
During early pregnancy, **repeat serologic screening** in previously seronegative pregnant women at the end of the first trimester (or until week 20) would **identify maternal primary CMV infection**

In the event of seroconversion, parents should be informed of the risk of vertical transmission and the possible consequences

Laboratory diagnosis of CMV infection during pregnancy

- **In the case of anti-CMV IgM+/IgG+ – IgG avidity testing at the 6-18th weeks of gestation** (sensitivity 94.3%, specificity 100%)
  - High avidity index – past CMV infection
  - Low or equivocal avidity index – primary CMV infection
- **After 20 weeks of gestation the sensitivity of avidity testing - decreased** (62.5%)

Our aims…



- **Started a routine CMV serology screening among pregnant women**
  - Participation - voluntary
  - Informed pregnant women about our aims and screening (oral and written statement)
  - Screening performed before 16 weeks of gestation
  - Validated anonymous questionnaire (ID of ethical permission: 3720/2016)
- **Two-step screening: primary screening and follow up**
  - anti-CMV IgM negative/anti-CMV IgG positive – stop
  - anti-CMV IgM positive/anti-CMV IgG positive – IgG avidity testing
  - anti-CMV IgM negative/anti-CMV IgG negative – offer regular follow-up every second month till delivery

Methods

Cytomegalovirus ELISA IgM Capture (Vircell, Spain) M1004

Cytomegalovirus ELISA IgG (Vircell, Spain) G1004

VIDAS CMV IgG ELFA (CMVG) (bioMérieux)

VIDAS CMV IgG Avidity II ELFA (CMVA) (bioMérieux)

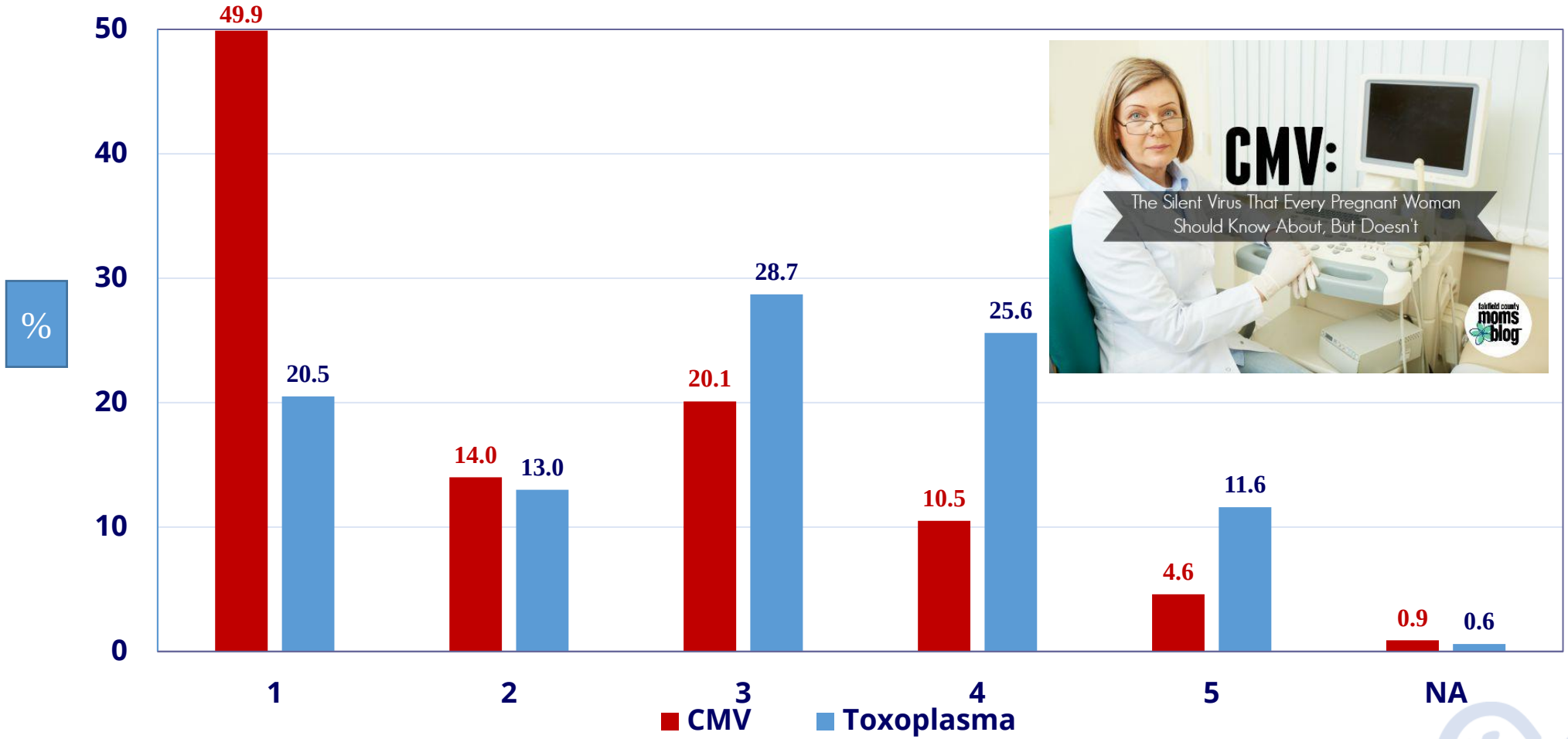
Demographical data about pregnant women (N=1,158)

Age (yr)	13-44
Average (yr)	30.72
County	
Csongrád-Csanád	1,148 (99.1%)
Others	6 (0.5%)
Not responding	4 (0.3%)
Type of residance	
Town	971 (83.9%)
Village	186 (16.1%)
Not responding	1 (0.09%)
Marrital status	
Single	180 (15.5%)
Married	790 (68.2%)
Partnership	177 (15.3%)
Not responding	11 (0.9%)

Demographical data about pregnant women (N=1,158)

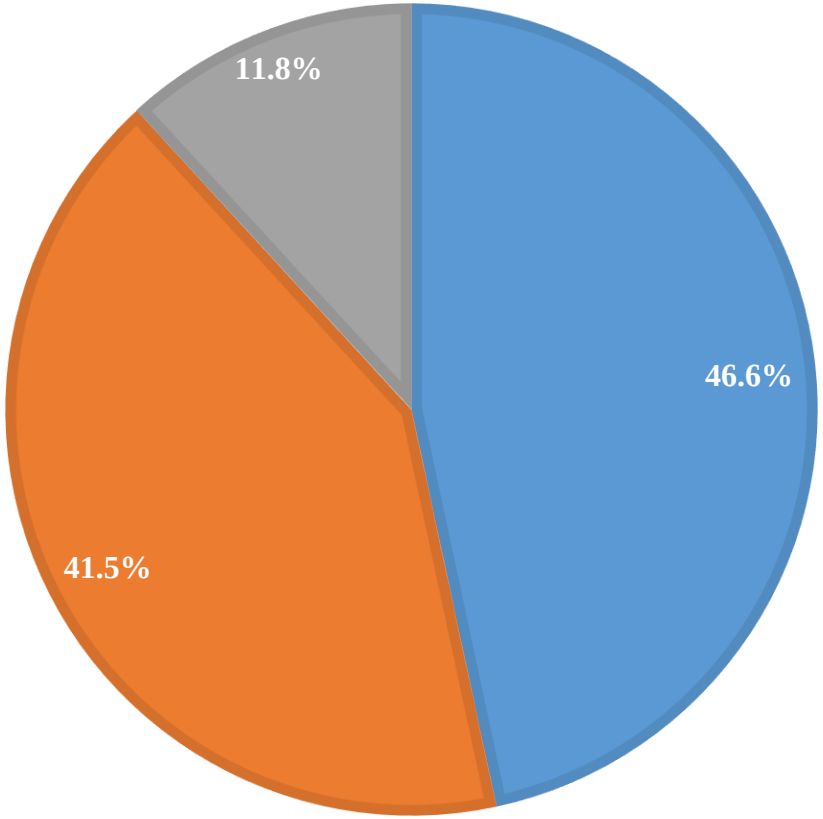
Number of previous pregnancy	Pregnant women (%)	Number of live births	Pregnant women (%)	Number of children under the age of 18 in the family	Pregnant women (%)
0	459 (39.6)	0	586 (50.6)	0	587 (50.7)
1	390 (33.7)	1	393 (33.9)	1	385 (33.2)
2	178 (15.4)	2	148 (12.8)	2	153 (13.2)
3	72 (6.2)	3	17 (1.5)	3	13 (1.1)
4	28 (2.4)	4	4 (0.3)	4	3 (0.3)
5	17 (1.5)	5	3 (0.3)	5	1 (0.1)
6	5 (0.4)	NA	7 (0.6)	NA	16 (1.4)
7	1 (0.1)				
10	1 (0.1)				
NA	7 (0.6)				
Total	**1158 (100)**	**Total**	**1158 (100)**	**Total**	**1158 (100)**

A five-grading system for the evaluation of knowledge about CMV and toxoplasmosis (N=1,158)

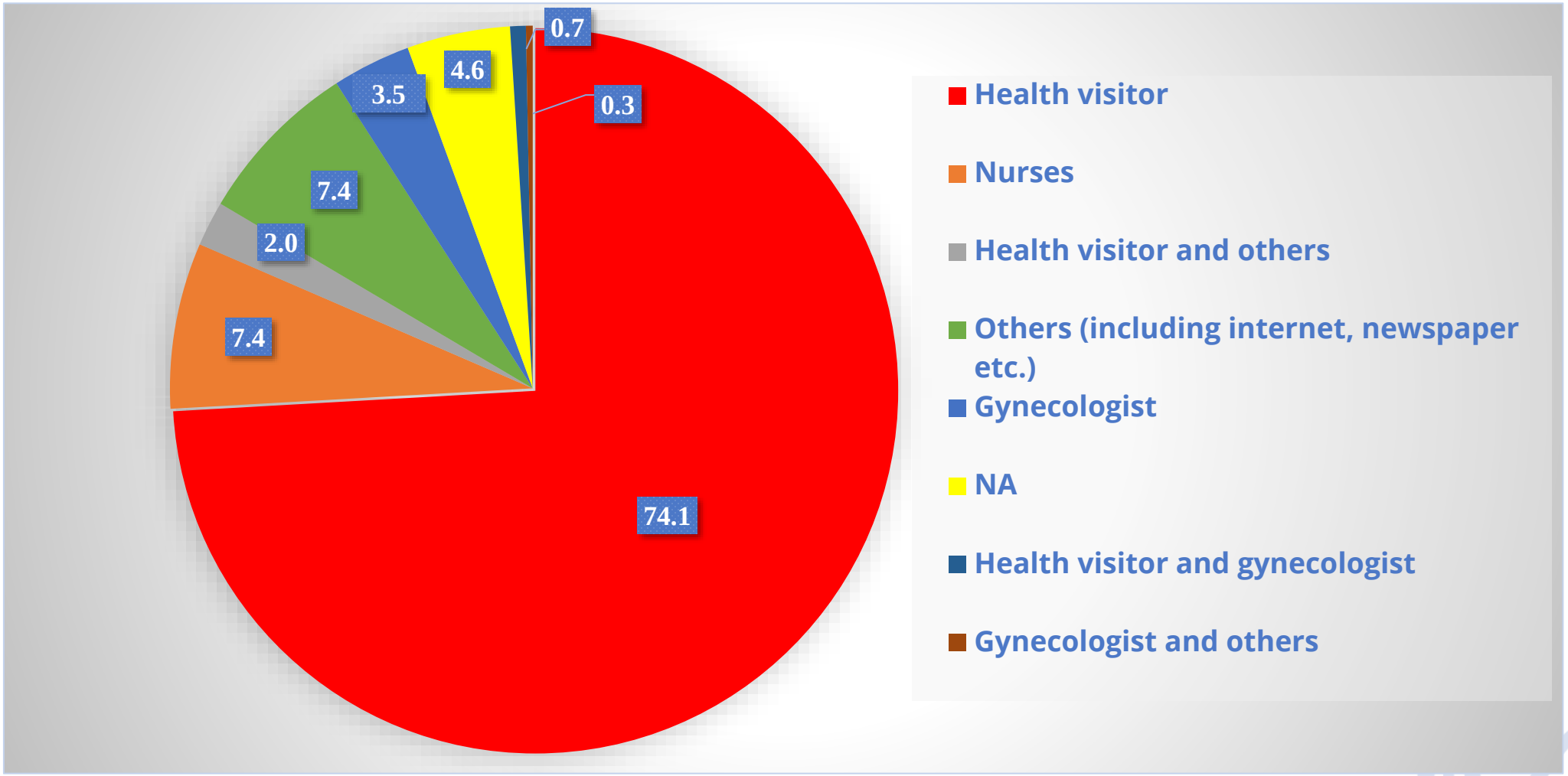


1-bad; 2-poor; 3-fair; 4-good; 5-excellent

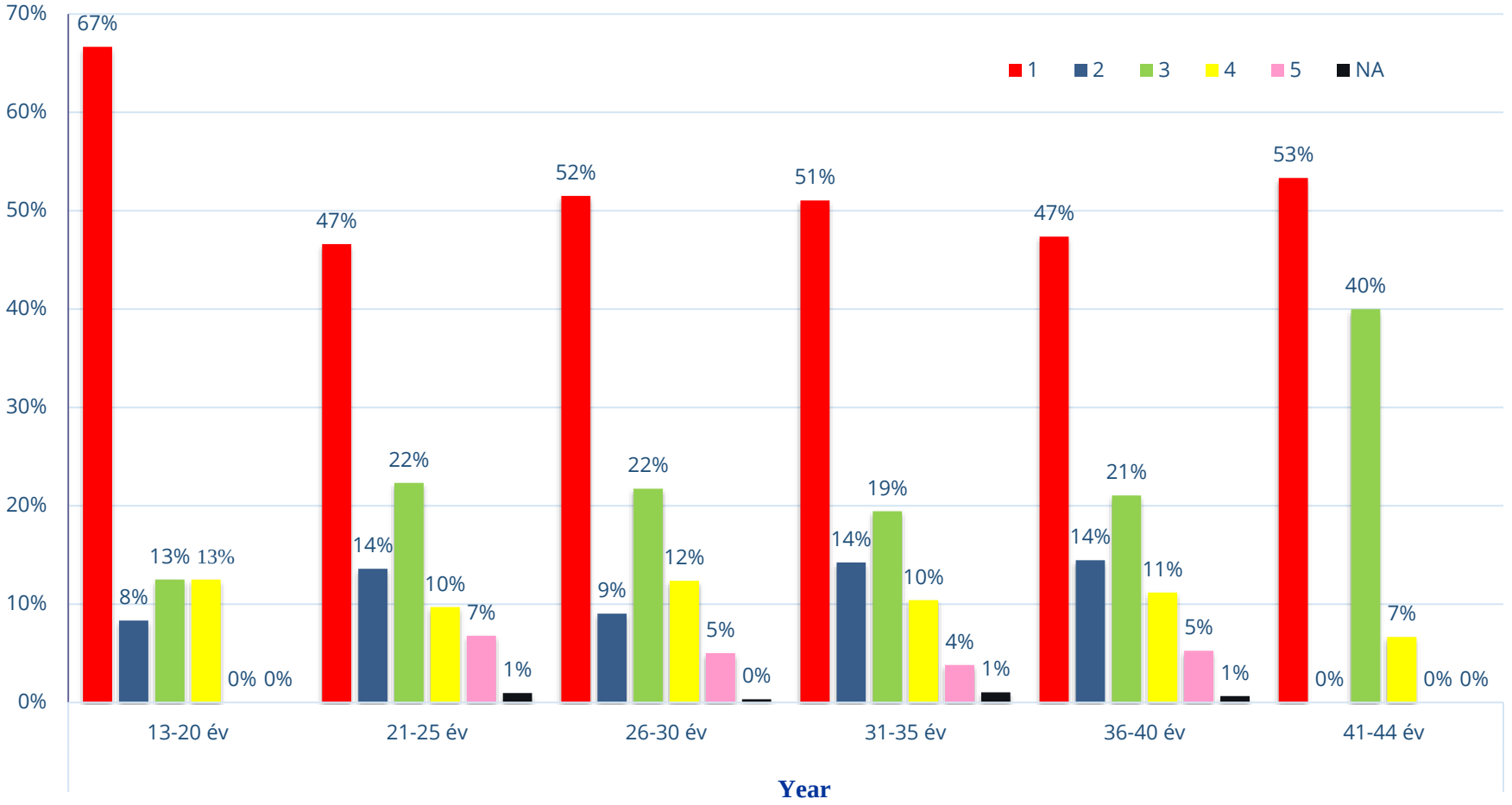
"Did you get information about the harmful effects of CMV on your baby?„ (N=1,158)



"Who gives information to you about the harmful effects of CMV on the fetus?" (N=540)



Knowledge about the possible harmful effects of CMV on fetuses according to the age of pregnant women (N=1,158)



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Results of CMV serological screening

Examination	Number of examined specimens (n=1,388)		Number of patients (n=1,231)	
	Negative	Positive/equivocal	Negative	Positive/equivocal
Anti-CMV IgM	1,380 (99.4%)	8 (0.6%)	1,225 (99.5%)	6 (0.5%)
Anti-CMV IgG	542 (39.1%)	846 (60.9%)	408 (33.1%)	823 (66.9%)

- **CMV seroprevalence 67%** (France 43.7%; Italy 68,3%; Norway 59.9%*)
- **Anti-CMV IgM positive/equivocal**: 6 patients

*Dieynaba *et al*. *Plos One* (2014)

Evaluation and interpretation of anti-CMV IgM positive/equivocal results

Patient 1: False positive anti-CMV IgM, lack of seroconversion – worsening of rheumatoid disease

27th January CMV IgM (i=19.6) positive, CMV IgG (i=0.9) negative

6th February CMV IgM (i=8.9) negative, CMV IgG (i=1.5) negative

14th March CMV IgM (i=5.2) negative, CMV IgG (i=0.9) negative

Patient 2: Past CMV infection

25th October CMV IgM (i=9.6) equivocal, CMV IgG (i=>200) positive, CMV IgG avidity index: high

Patient 3: Acute CMV infection – date of primary infection is uncertain

13rd May CMV IgM (i=16.3) positive, CMV IgG (i=34.9) positive, CMV IgG avidity index: equivocal

23rd September CMV IgM (i=10.1) equivocal, **CMV IgG (i>200) positive, CMV IgG avidity index: high**

Patient 4: Acute CMV infection – date of primary infection is uncertain – abortion

12th January CMV IgM (i=12.0) positive, CMV IgG (i=63.8) positive, CMV IgG avidity index: equivocal

Patient 5: Acute CMV infection – after birth newborn baby tested for CMV (CMV PCR urine/plasma: negative)

16th January CMV IgM (i=29.8) positive, CMV IgG (i=31.4) positive, CMV IgG avidity: low

Patient 6: Past CMV infection – after the 18th week of gestation miscarriage happened

15th August. CMV IgM (i=28.4) positive, CMV IgG (i=84.6) positive, CMV IgG avidity index: high

Our summary and recommendations

CMV seroprevalence in Hungary similar to seroprevalence data from other European countries

Low anti-CMV IgM positivity in specimens collected until 16th weeks of gestation

High interest during the primary screening

Low interest during the follow-up (only 96 of 408 seronegative patients were enrolled in control serology testing)

Knowledge about the possible effects of CMV infection on fetuses – poor – **education and hygiene recommendations to prevent CMV infection should be made to all pregnant**

RECOMMENDATIONS FOR DIAGNOSIS	
Primary infection in pregnant women	IgG, IgM, IgG avidity if positive IgM and IgG
Non-primary infection in pregnant women	No tools validated
Fetal infection	CMV PCR in amniotic fluid after 20 weeks and more than 8 weeks after presumed onset of maternal primary infection
Neonatal infection	CMV PCR in saliva or urine collected in the first 3 weeks of life
Retrospective diagnosis in toddlers with compatible symptoms	CMV PCR in neonatal DBS
RECOMMENDATIONS FOR SCREENING AND PREVENTION	
Primary prevention of maternal primary infection	Information for pregnant women on cCMV and application of hygienic measures to prevent maternal infection
Infection in pregnant women	No recommendation for screening Information for pregnant women on cCMV and application of hygienic measures to prevent maternal infection
Universal neonatal screening	No recommendation
Targeted testing in neonates who failed universal hearing screening	CMV PCR in saliva (if positive, confirm in urine or by DBS PCR if the infant is > 3 weeks of age)

(c)CMV, (congenital) cytomegalovirus; DBS, dried blood spot; Ig, immunoglobulin; PCR, polymerase chain reaction.

Congenital Cytomegalovirus Infection: A Narrative Review of the Issues in Screening and Management From a Panel of European Experts

Tiziana Lazzarotto[1], Daniel Blázquez-Gamero[2], Marie-Luce Delforge[3], Ina Foulon[4], Suzanne Luck[5,6], Susanne Modrow[7] and Marianne Leruez-Ville[8]*

Thank you for your attention!

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