London's Global University

UCL

Screening for Congenital CMV Infection

Venice

April 25 2016

Paul D Griffiths MD DSc FRCPath

Professor of Virology

UCL Institute of Immunity and Transplantation

Overview

Definition

Criteria

Potential benefits

Comparison with other conditions

How screen?

- Universal
- Selective

What specimen?

- DBS
- Saliva

Definition of Screening

The systematic application of a test to identify asymptomatic individuals at risk of a specific disorder in order to prompt further investigation or preventative action

Benefits must outweigh harms

Wald N. J Med Screen, 15, 50, 2008.

Does CMV meet criteria for screening?

Common problem ✓

Serious problem ✓

Natural history defined ✓

Confirmatory tests ✓

Effectiveness of screening?

Acceptability of screening?

- Health care providers
- parents

Cost-effective?

Grosse S. J Clin Virol, 2009.

Evaluating Conditions Nominated for Newborn Screening

Is there definitive evidence that screening leads to improved outcome?

If no, consider:

- **Is the natural history defined?**
- **Is there a valid screening test?**
- **Is the clinical validity defined?**
  - **Sensitivity and specificity**
- **What is the clinical utility?**
  - **Benefits**
  - **Harms**
- **Are screening, diagnosis and treatment cost-effective?**

Calonge. Genetic Med, 12, 153, 2010.

Potential benefits

- RCT of ganciclovir ✓
  - Recruited symptomatics, CNS
  - Prevents future disease
    - Pre-emptive therapy
- RCT of valganciclovir ✓
  - Recruited symptomatics
  - VGCV well tolerated
- Now consider RCT in asymptomatics?

Consider a RCT

Asymptomatics

Compare VGCV with controls

- **Screening**
- **RCT**

Placebo

6 weeks?

6 months or other?

Whole Blood Viral Load

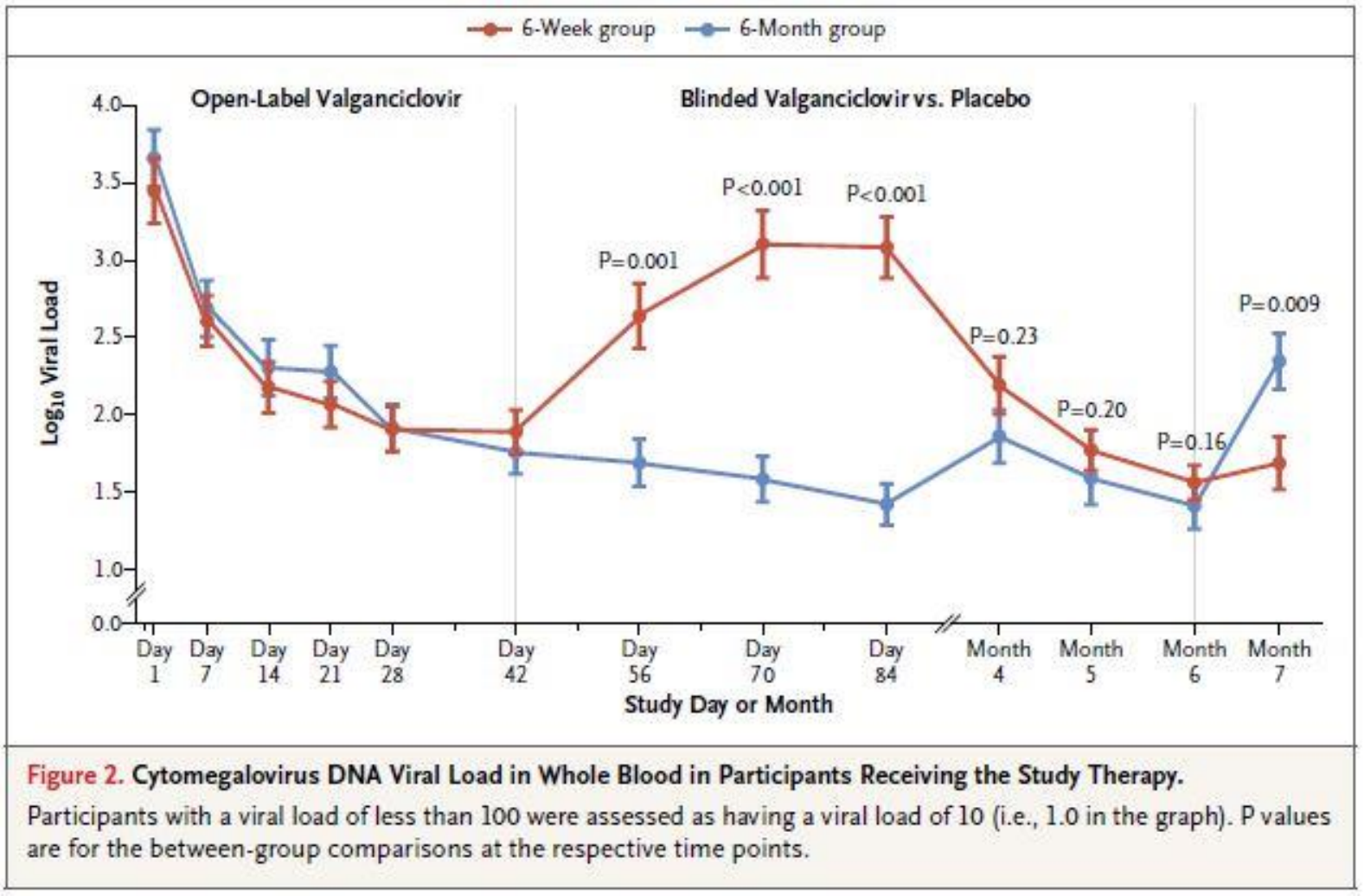
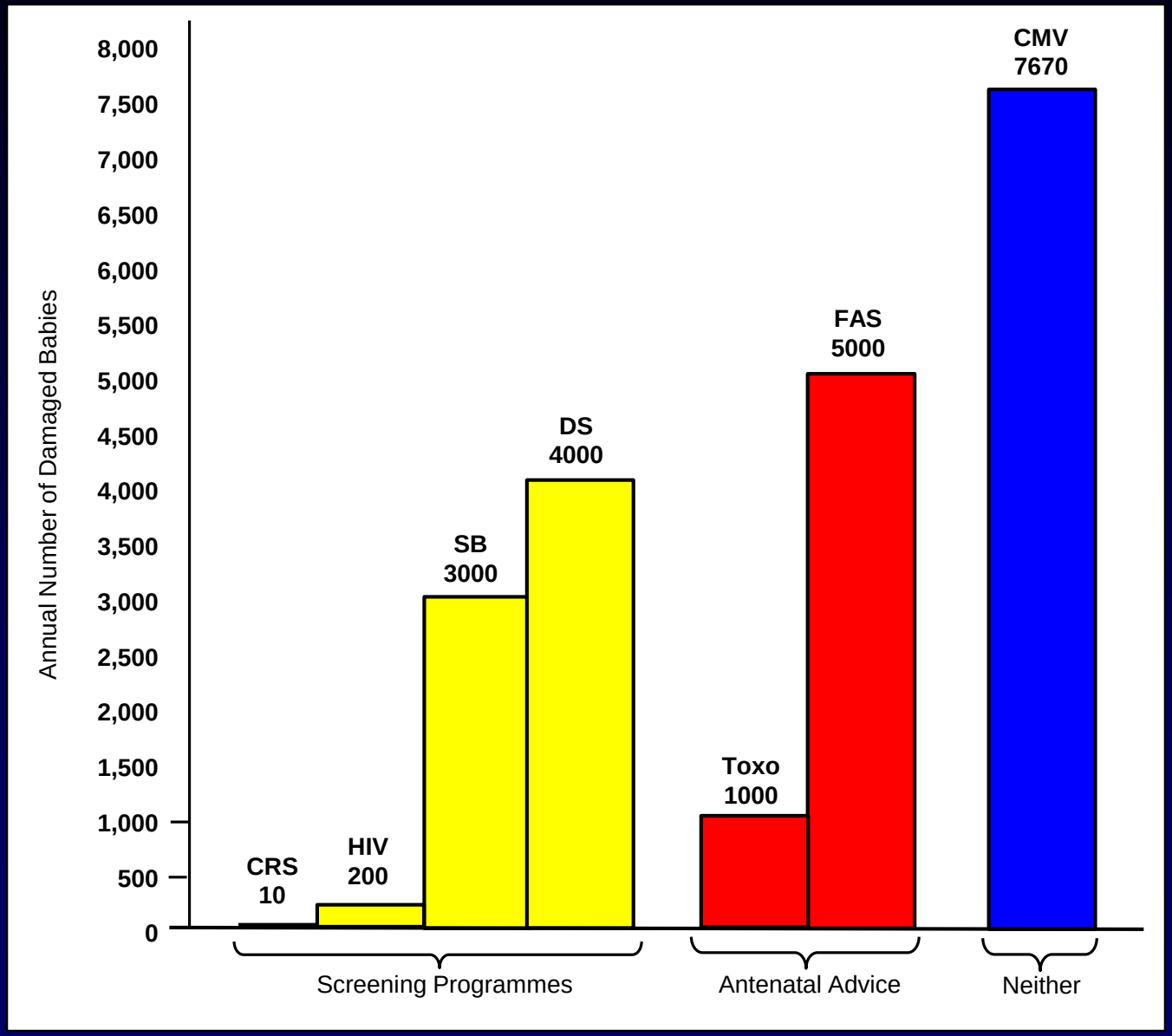


Figure 2. Cytomegalovirus DNA Viral Load in Whole Blood in Participants Receiving the Study Therapy.

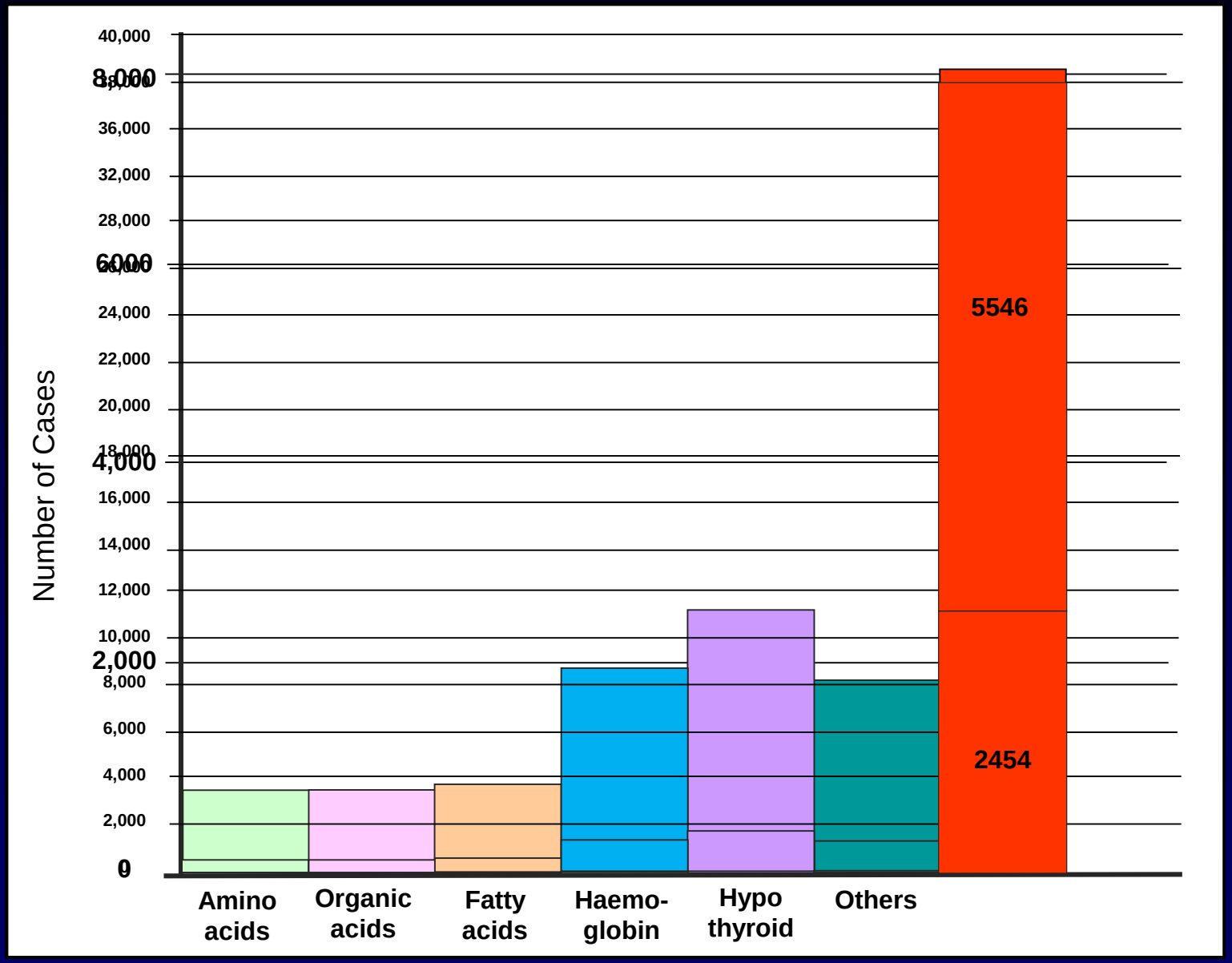
Participants with a viral load of less than 100 were assessed as having a viral load of 10 (i.e., 1.0 in the graph). P values are for the between-group comparisons at the respective time points.

Comparison with other conditions



Cannon M. BMC Pub Hlth, 5, 70, 2005. Dollard, S. RMV, 17, 355-362, 2007. Wang, C. Clin Inf Dis, 52, e11-e13, 2011.

Annual Cases in USA of 27 Conditions now Screened for in Most States (total 6,618 cases)



MMWR. 57,1012-1015, 2008. Dollard, S. RMV, 17, 355-362, 2007. Wang, C. Clin Inf Dis, 52, e11-e13, 2011.

DBS Screening

Rapid DEAFF of saliva

PCR run with:

- **Single primer set**
- **Dual primer set**

11,422 neonates single primer:

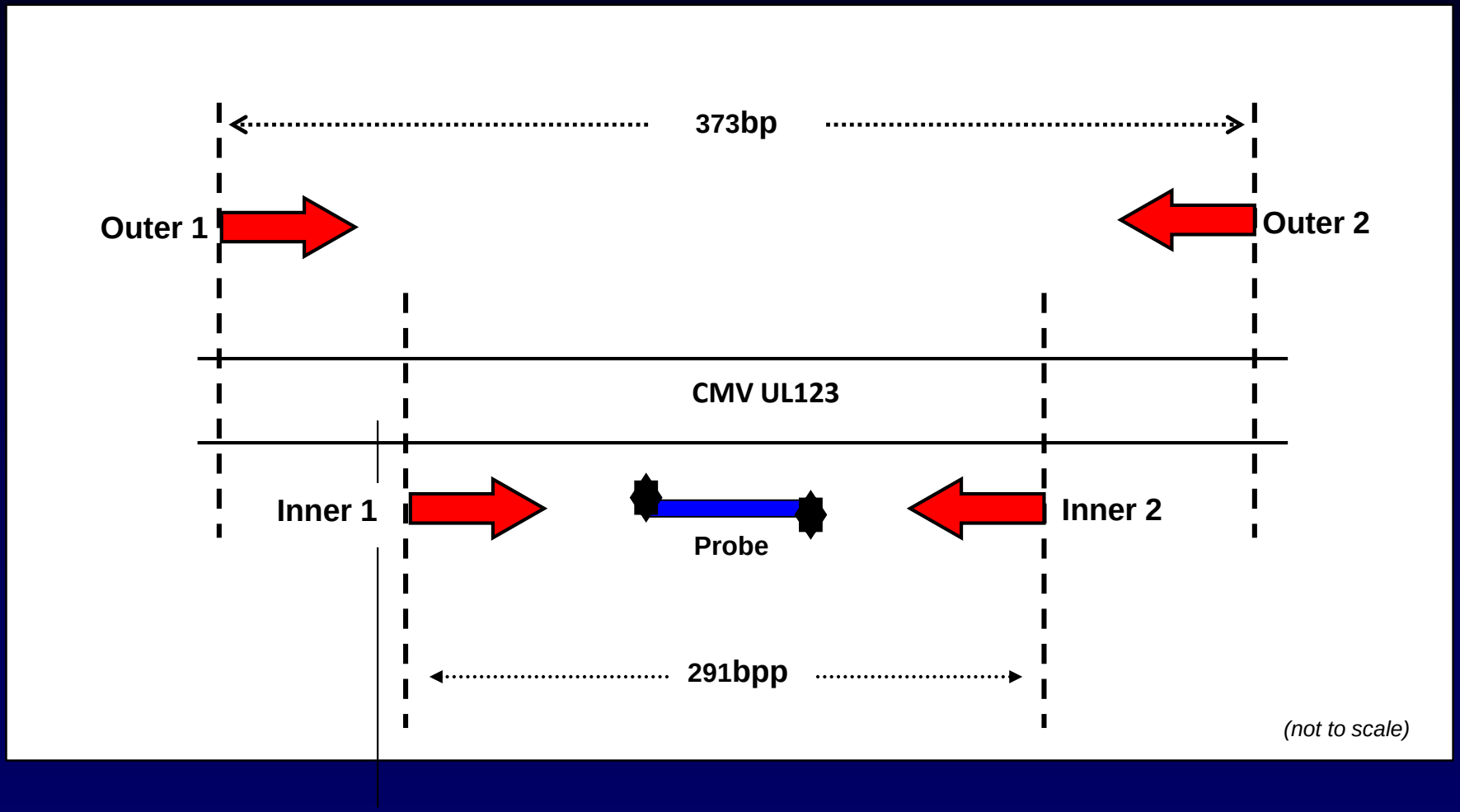
- **17/60 (28%) sensitivity**

9,026 neonates dual primer:

- **11/32 (34%) sensitivity**

Boppana SB. JAMA, 303, 1375, 2010.

Schematic Diagram of Single Tube Nested PCR



Atkinson CE. J Viro Meth, epub 13.10.2013.

Saliva PCR Screening

Rapid DEAFF of saliva

PCR of saliva without DNA extraction:

- **Transport medium, 4^0C**
- **Dried swab, RT**

17,622 neonates tested liquid PCR

- **85/85 (100%) sensitivity**
- **99.9% specificity**

17,327 neonates tested dry PCR

- **74/76 (97%) sensitivity**
- **99.9% specificity**

Boppana SB. NEJM, 364, 2111, 2011.

DBS vs Saliva

Shared features

- **Need PCR at screening centres**

DBS

- **Fits onto existing screening programme**
- **May be able to pick up many cases at risk of disease**
- **Smaller number of cases to be followed**

Saliva

- **Requires parallel system for collection and delivery**
- **Will identify more cases, many of which not at risk of disease**

CMV-related disability

Annual Number of:	Australia (population ~22 million)	England & Wales (population ~50 million)	USA (population ~307 million)
Live Births	296,600	709,000	4,248,000
Congenital CMV infections (0.6%)	1,780	4,254	25,488
Symptomatic at birth (12.8%)	228	544	3,262
Develop disability (50%)	**114**	**272**	**1,631**
Asymptomatic at birth (87.2%)	1,552	3,710	22,226
Develop disability (13.5%)	**210**	**501**	**3,001**
Total CMV-related disabilities	**324**	**773**	**4,632**

Cannon MJ. Rev Med Virol, 24, 291 – 307, 2014.

Screening for CMV and Hearing Loss in USA

Symptomatic at Birth	No Benefit	Benefit
▪ Diagnosed clinically	815	
▪ Not diagnosed but no HL	1,504	
▪ Not diagnosed but HL		943

Asymptomatic at Birth	No Benefit	Benefit
▪ No HL	19,514	
▪ HL		2,712

Cannon MJ. Rev Med Virol, 24, 291 – 307, 2015.

Selective Screening with Written Consent

Newborns with “no clear responses” on hearing screen

- **Saliva and urine requested for PCR**
- **Baseline and 3 month maternal anxiety measured**

411 recruited

99% returned a sample

- **99% saliva**
- **50% urine**

6 cases congenital CMV detected

- **All within 23 days of birth**
- **5/6 assessed for VGCV within 31 days**

Anxiety not increased in mothers

Williams. ADC epub 2014.

Selective Screening as a Routine

Newborns with “no clear responses” on hearing screen

- **Hearing screeners trained to collect saliva**

203/255 eligible newborns had swab taken

PCR results available within 31 days

Two cases of congenital CMV identified

- **Reviewed by paediatrician within 10 days**

Kadambari S Eur J Peds 2015

Selective Screening: cost effectiveness

Costs of identification

- **Screener time, swab, PCR, administration time**

Costs for identified cases

- **Paediatrician, laboratory tests, imaging, ophthalmology**

Costs for treating some

- **VGCV 6 weeks, monitoring bloods, paediatrician, ophthalmology**

Costs for following asymptomatics

- **Paediatrician, audiology**

Total per treated case = £6,683

Total per improved hearing outcome = £14,202

Williams Arch Dis Child F501, 2015

Summary

Needs input on several fronts

- **Laboratory assays**
- **Cohorts to evaluate assays**
- **Demonstration screening projects**
  - **Universal**
  - **Selective**
- **RCT of VGCV in asymptomatics**
- **Multidisciplinary interactions**