UKCSNS MCADD

UK Collaborative Study of Newborn Screening
Medium chain acyl CoA Dehydrogenase Deficiency
• Collaborating with the BIMDG, UKNSLN and Oxford University •
• Funded by the Department of Health and National Screening Committee •

Newborn Screening for MCADD Deficiency

Experience of a Pilot QA Scheme

Professor Anne Green
on behalf of the study collaborators

Belfast
October 2006

NHS

Outline

- **The Screening Study**
- **The Screening Test**
- **Quality assurance**
  - External QA scheme
  - Population data
- **Evaluation against the NSC criteria**

Study Objectives

- Screening Test performance
- MCADD phenotypes ascertained by screening
- Clinical outcomes
- Costs and cost effectiveness
- Psychosocial outcomes

Study Design

- Prospective observational multicentre study
  - **Screening for 24 months in 6 UK screening laboratories**

- Screening test
  - **octanoylcarnitine (C8) measured in dried blood spots taken between 5-8 days of age**
  - **C8 ≥ 0.5µmol/L → REFERRAL**

- Diagnostic confirmation
  - **Repeat C8**
  - **Urinary hexanoylglycine**
  - **Mutation analysis (2 stage)**

- Agreed Clinical and Dietary Management protocol

Results:
March 2004-February 2006

- ~745,387 babies screened
- 105 presumptive positive cases notified
- Screen positive prevalence:
  ~ 1.4 per 10,000 (95% CI 1.1, 1.7)

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- 48 homozygous 985A>G of 103 screened positives (47%)
- 127 of 206 alleles 985A>G from 103 completed cases (62%)

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- 48 homozygous 985A>G of 87 confirmed MCADDs (55%)

- 116 985A>G of 174 alleles from confirmed MCADDs (67%)

Study

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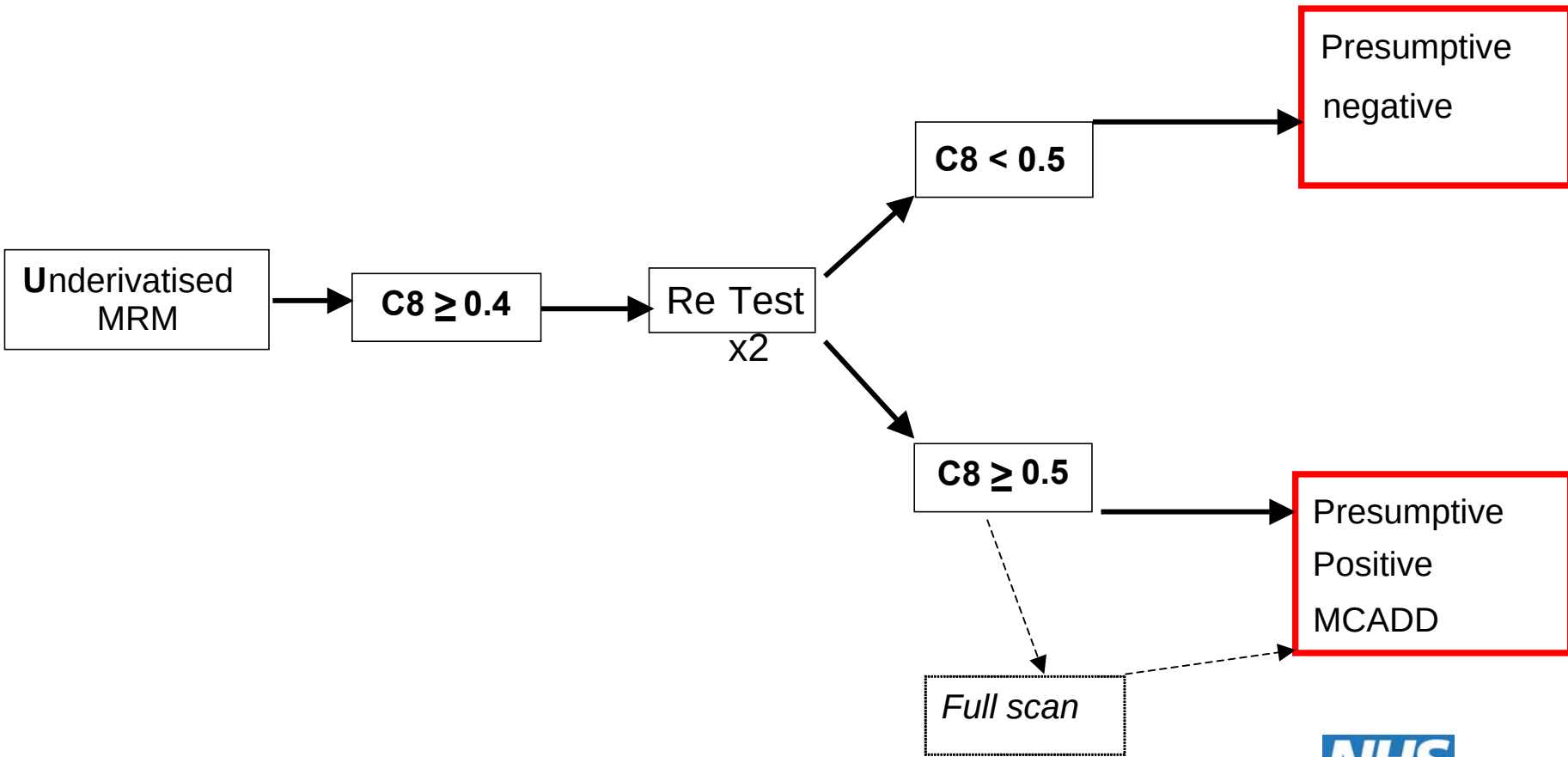
Screening algorithm



NSC Criteria – The Test

- There should be a simple, safe, precise and validated screening test
- The distribution of test values in the target population should be known and a suitable cut off level defined and agreed
- The test should be acceptable to the population

Quality Components

- **Standardize methodology**
  - Underivatized
  - MRM
  - Assay ‘Conditions’ (QA Group)

- **Quality Assessment Schemes**
  - C8 & C0
  - DNA (for diagnosis)

- **Population Comparisons**

Acknowledgments

- Screening Lab Directors & Staff

- BCH Lab Team - QA schemes (C8,C0,DNA)
  - **Rachel Rayner**
  - **Pippa Goddard**
  - **Tim Hutchin**
  - **Sarah Ball**

- Study Centre – Population data analysis
  - **Pamela Phillips**
  - **Bianca Stanford**
  - **Juliet Oerton**
  - **Carol Dezateaux**

Quality Assessment Scheme for C8 &C0 across 6 Labs

Assessment of Precision

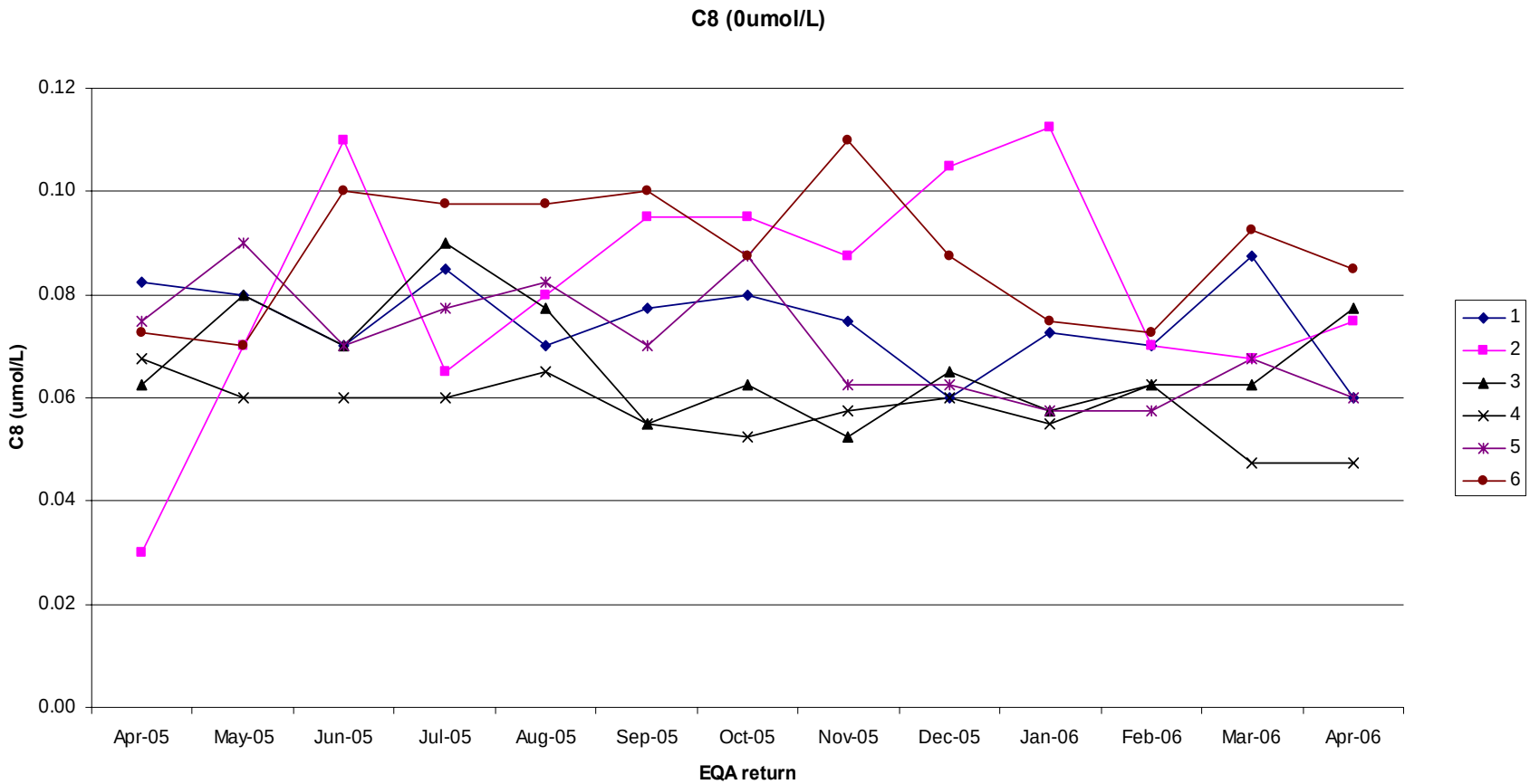
- **Specimens (dried blood spots) distributed monthly**
- **Mean of 4 analyses**

- CDC Samples (USA)

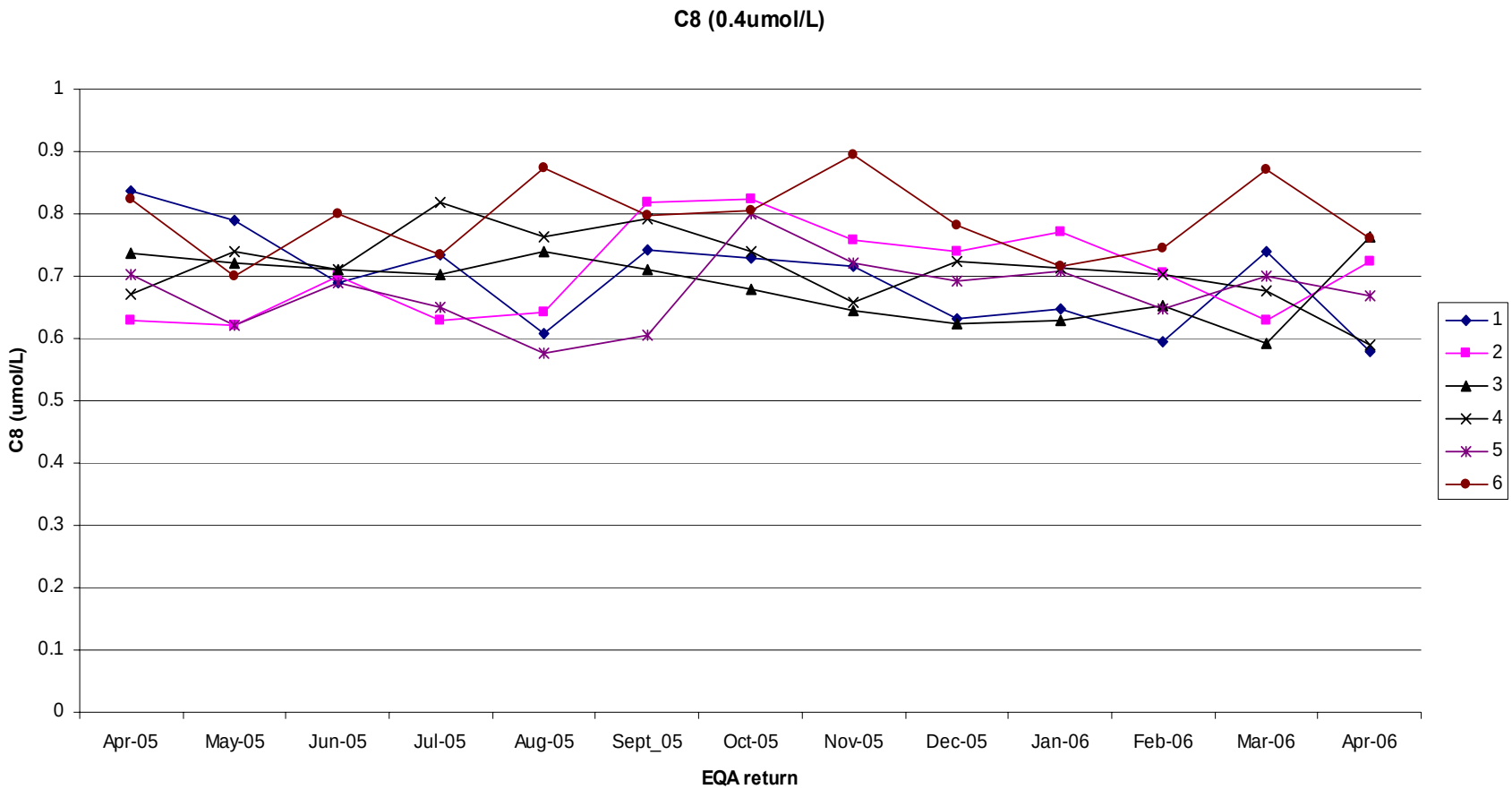
  0.5 μmol/L

- In House Specimens
  - **mixture of fresh-frozen plasma and packed cells, spiked with L-octanoyl carnitine & L carnitine**
  - **Since January 2005, single batch prepared specimens with added C8 (** 0.4, 1.5μmol/L) & **C0** (10, 80 μmol/L)

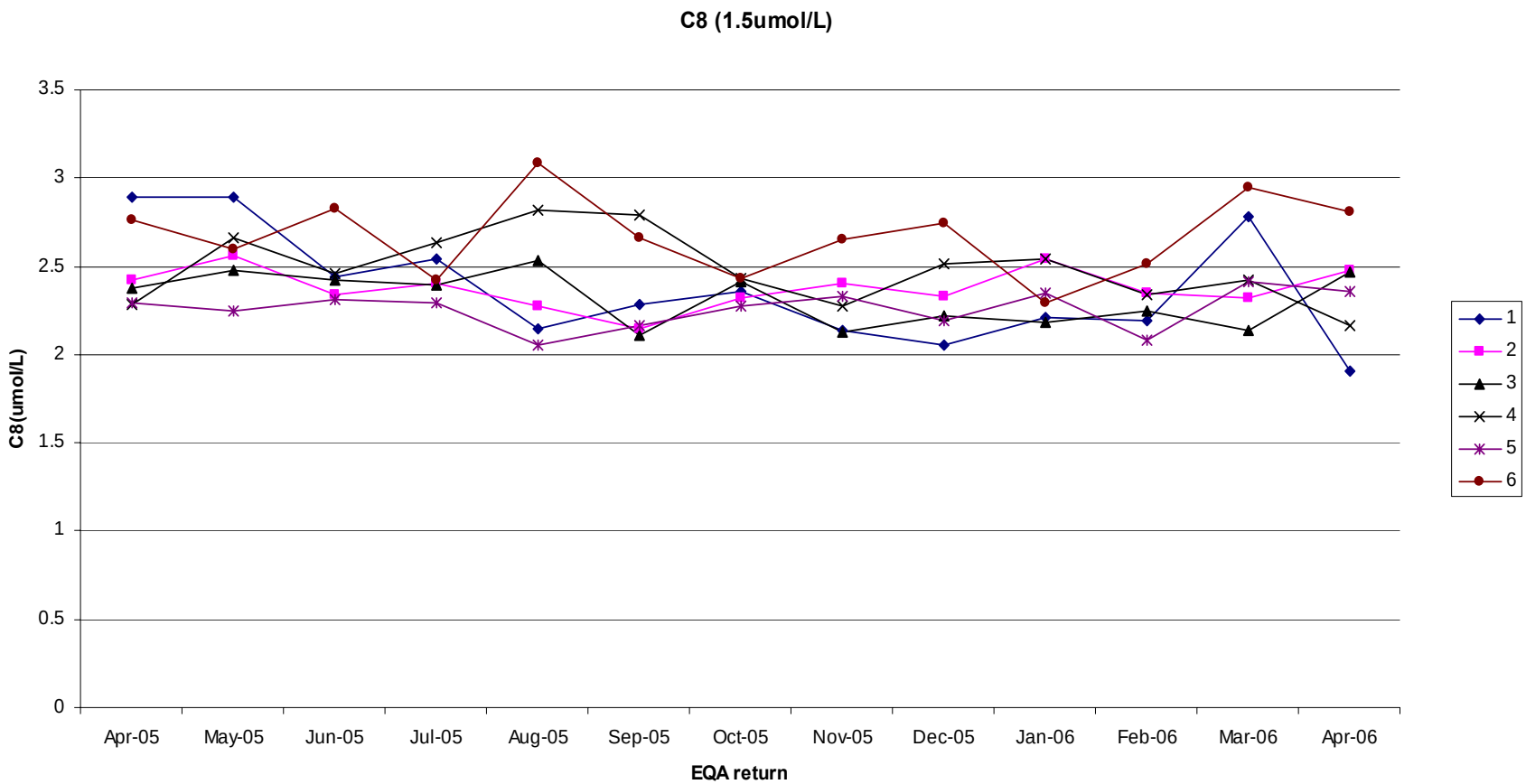
In House - C8 base 0μmol/L added



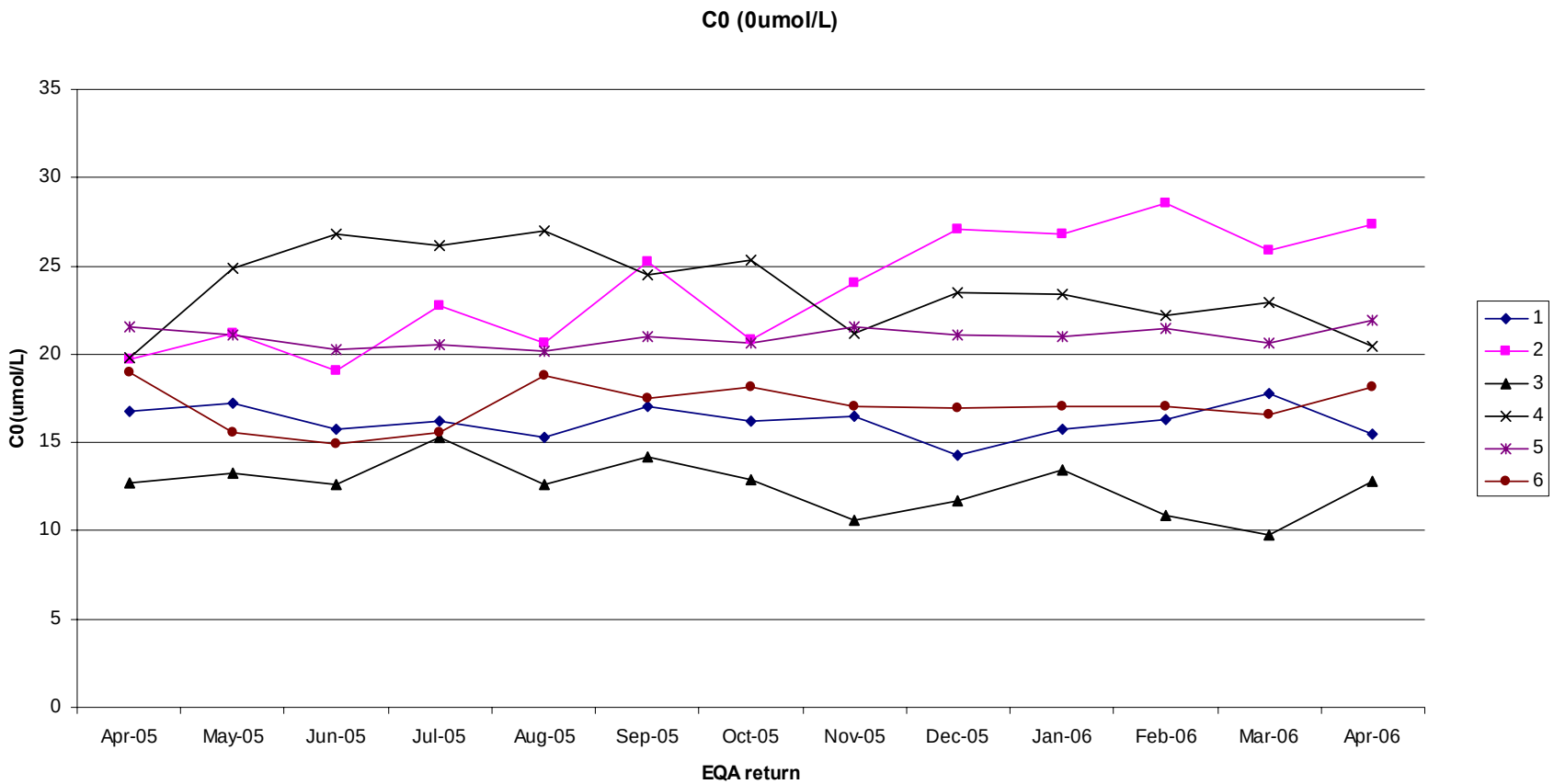
In House - C8 0.4μmol/L added



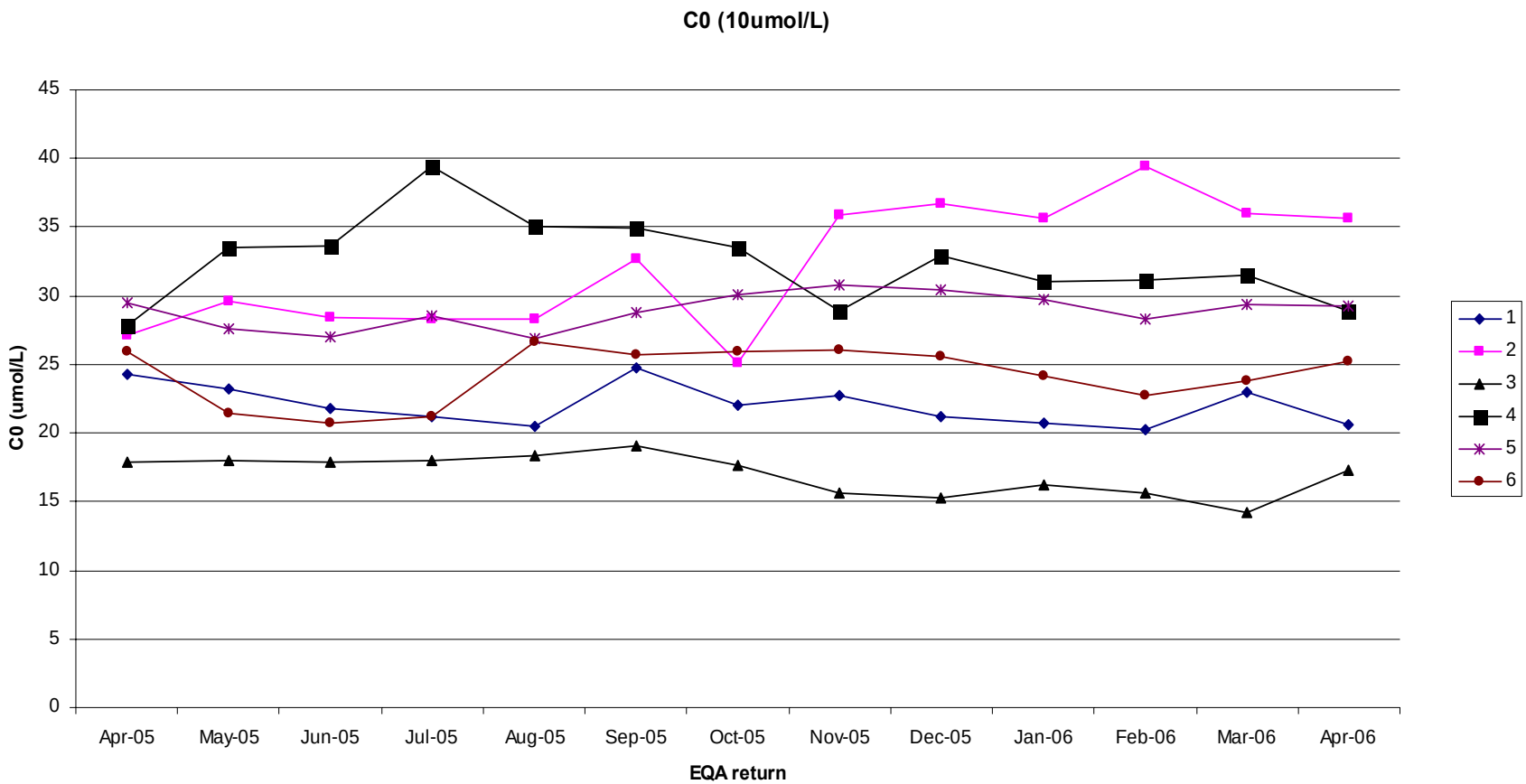
In House - C8 1.5µmol/L added



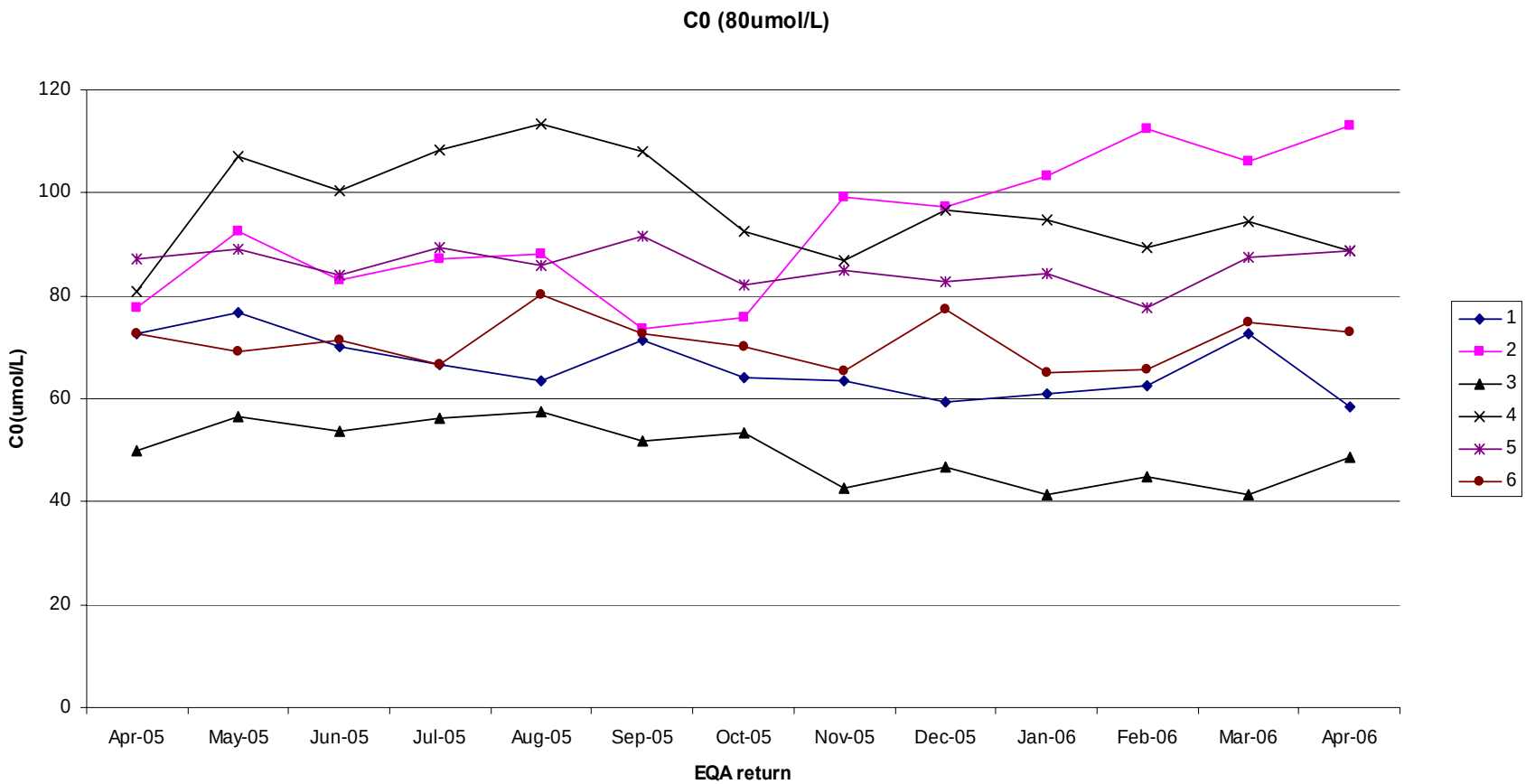
In House -C0 base 0μmol/L added



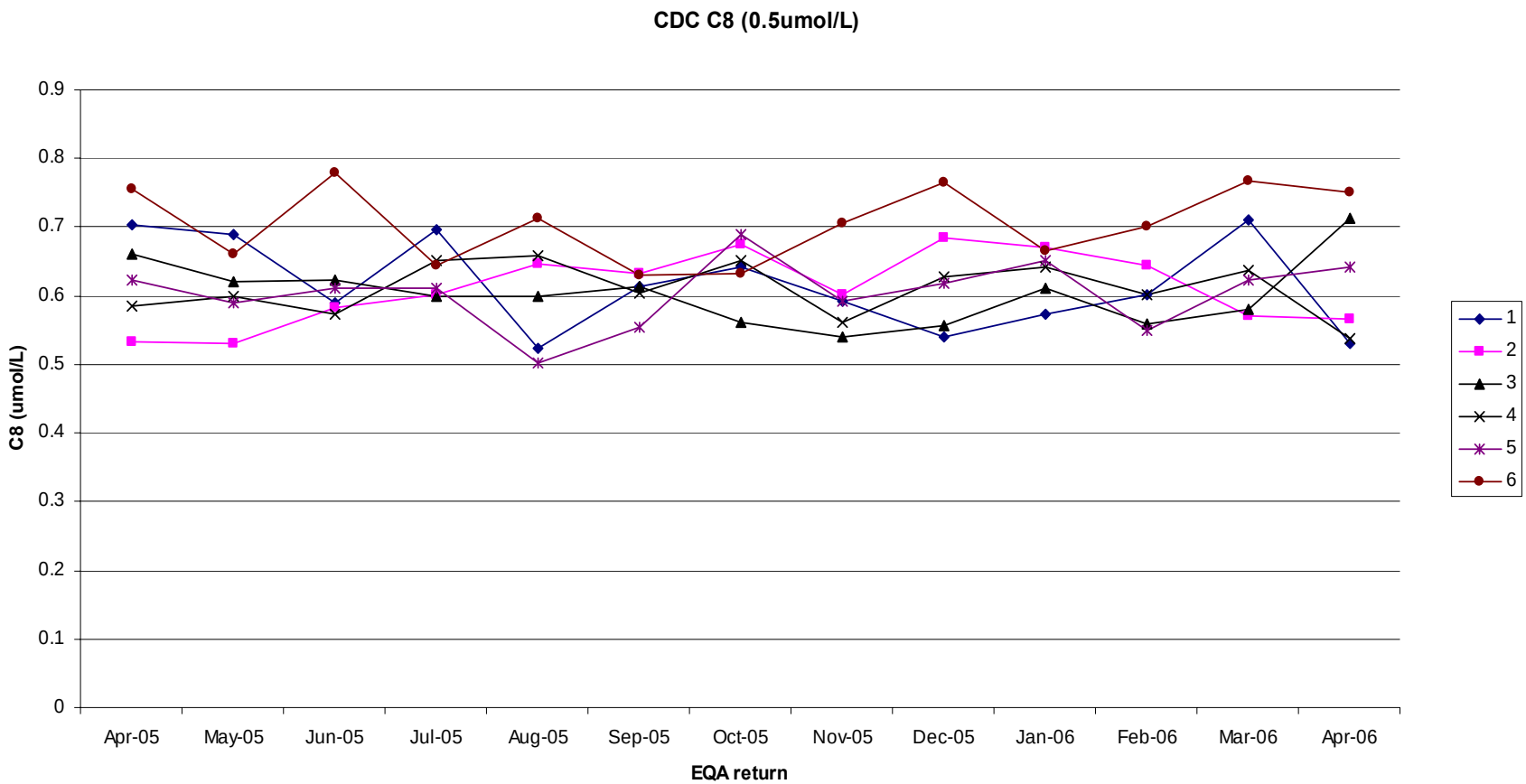
In House - C0 10μmol/L added



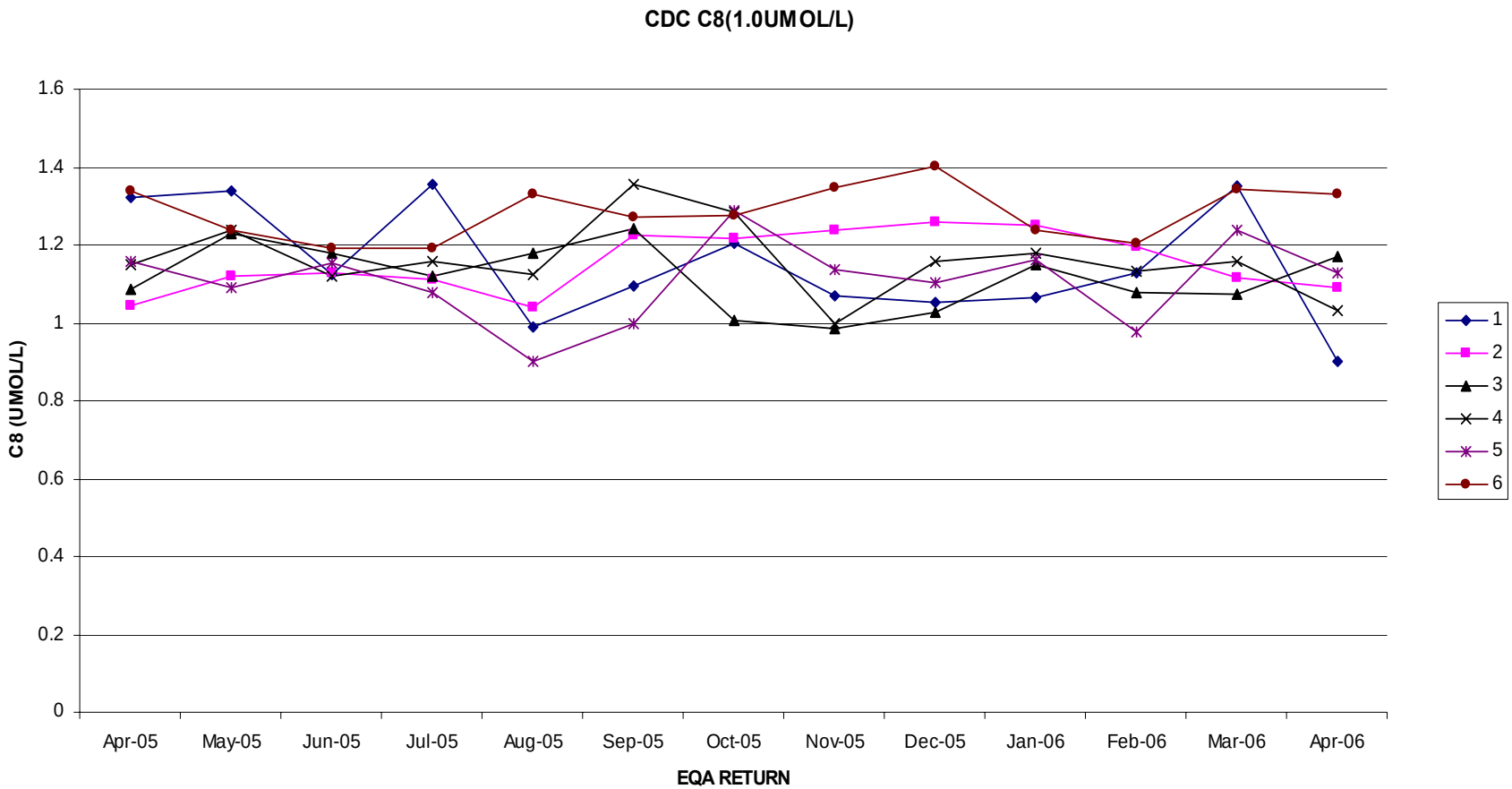
In House - C0 80μmol/L added



CDC - C8 0.5μmol/L added



CDC - C8 1.0μmol/L added



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Centile Table : July 2005

C8

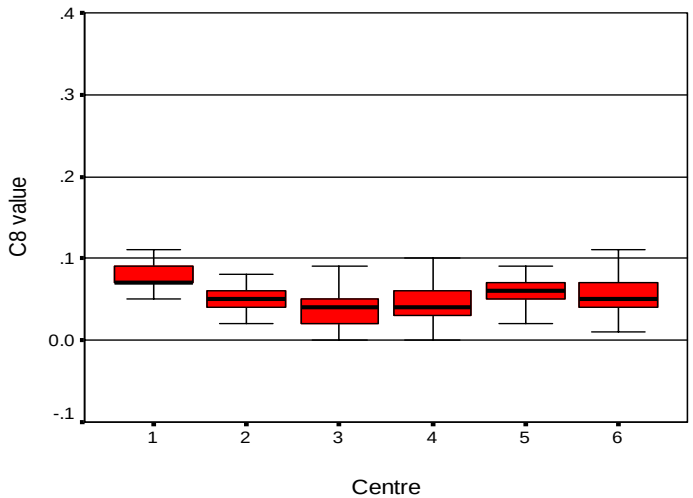
Values above 0.5 removed

Statistics

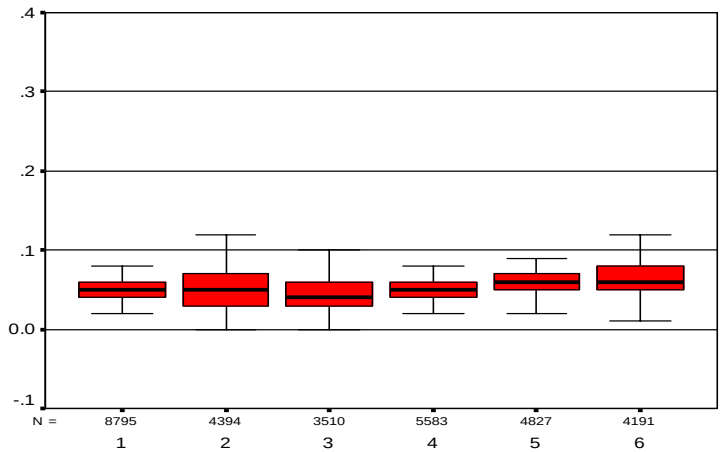
		1	2	3	4	5	6
N	Valid	9102	4585	3661	5713	5676	4261
Mean		.0581	.0809	.0420	.0489	.0588	.0778
Median		.0600	.0700	.0400	.0400	.0600	.0700
Minimum		.00	.01	.00	.00	.03	.01
Maximum		.24	.35	.27	.49	.32	.39
Percentiles	.5	.0300	.0300	.0000	.0200	.0300	.0300
	1	.0300	.0400	.0000	.0200	.0300	.0300
	5	.0300	.0500	.0100	.0300	.0400	.0400
	10	.0400	.0500	.0200	.0300	.0400	.0500
	25	.0500	.0600	.0300	.0400	.0500	.0600
	50	.0600	.0700	.0400	.0400	.0600	.0700
	75	.0700	.0900	.0500	.0600	.0700	.0900
	90	.0800	.1200	.0700	.0700	.0800	.1100
	95	.0900	.1400	.0800	.0900	.0900	.1300
	99	.1200	.1700	.1338	.1300	.1200	.1938

C8 population data comparisons

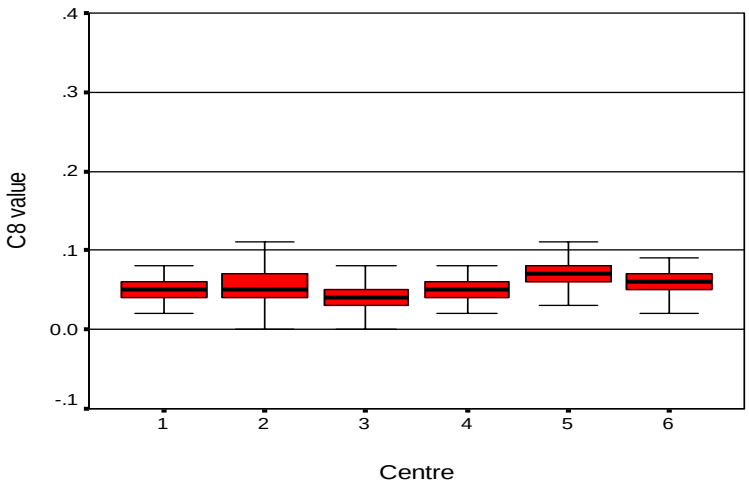
(6 Laboratories)



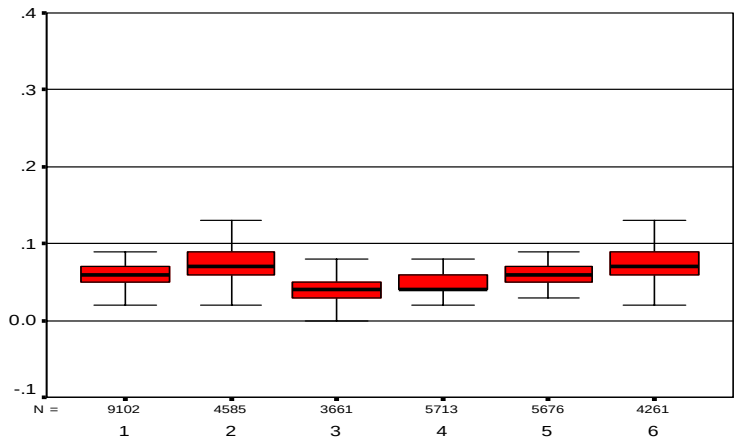
Dec 2004



May 2005

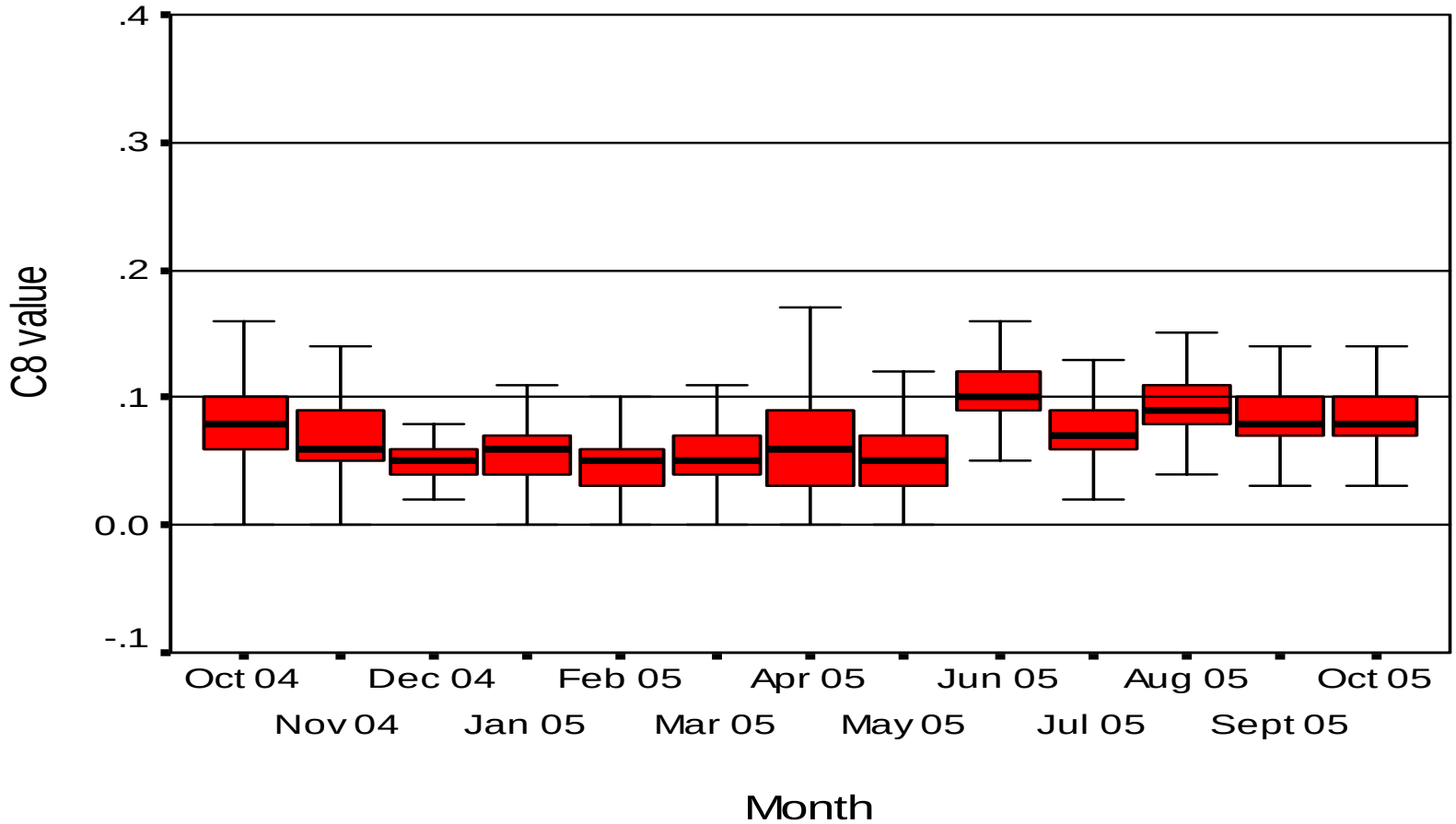


March 2005

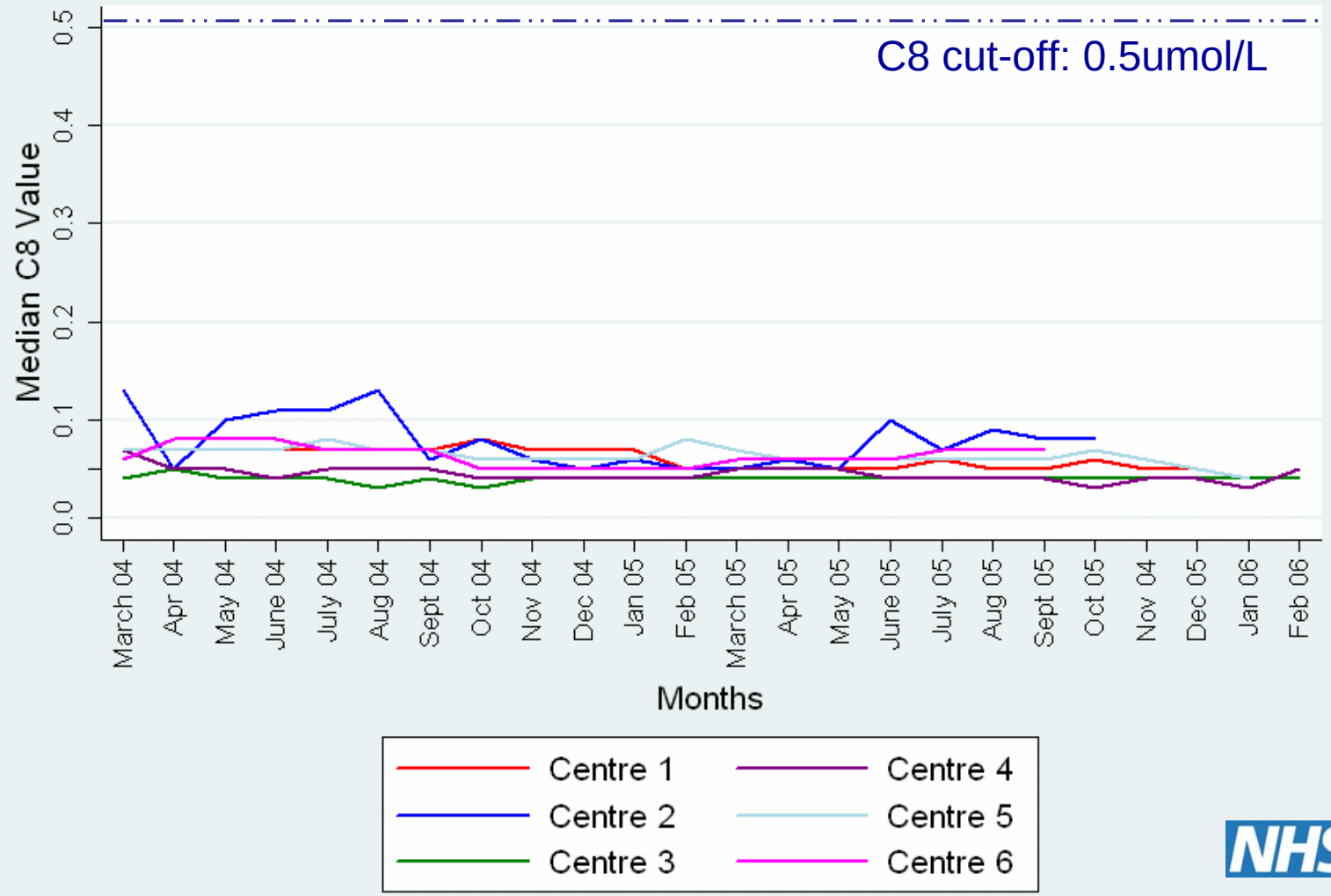


July 2005

Monthly Population Data – 1 Lab



Median C8 at Screening by Centre: March '04- Feb '06



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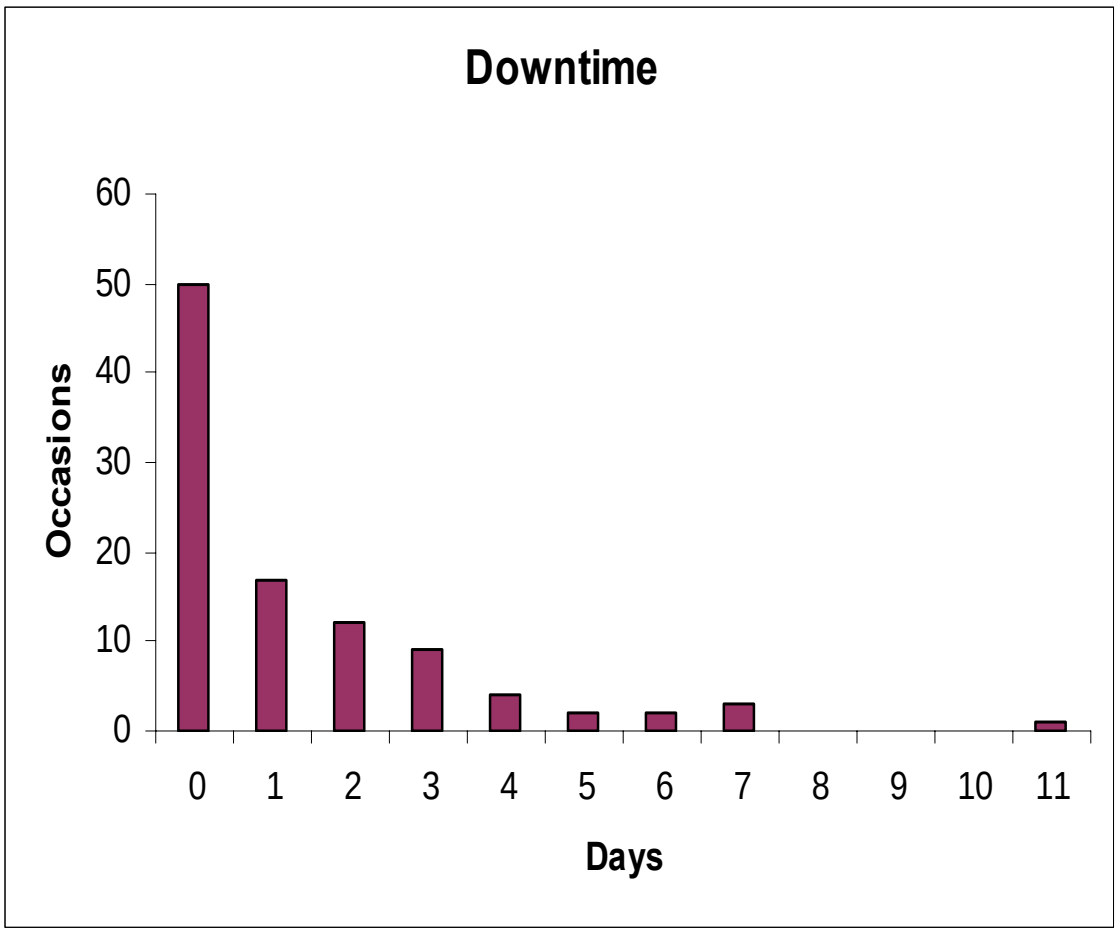
Evaluation of NSC Criteria for The Screening Test C8

- **Simple to add on to PKU screening by Tandem MS**
  - No extra blood
- **Suitable for large scale use**
  - Throuput (40 000 – 110 000 pa)
  - Speed
  - Reliability
- **Precise**
  - Reliable over time
  - Consistency between labs
  - Quality assured

Tandem Downtime

March 05 – June 06(6 labs over 16months)



- Total downtime - 138 days
- Average per lab – 23 days (n=6
  27 days (n=5)
- Back up used – 114 days
- No back up – 24days no service

Evaluation of NSC Criteria for The Screening Test C8

- **Population data**
  - Consistency between labs
  - Consistency over 24 months
  - Little variation with age

- **Validated cut off**
  - Well separated from population
  - Predictive value is high (few carriers, few false positives)

Study Results

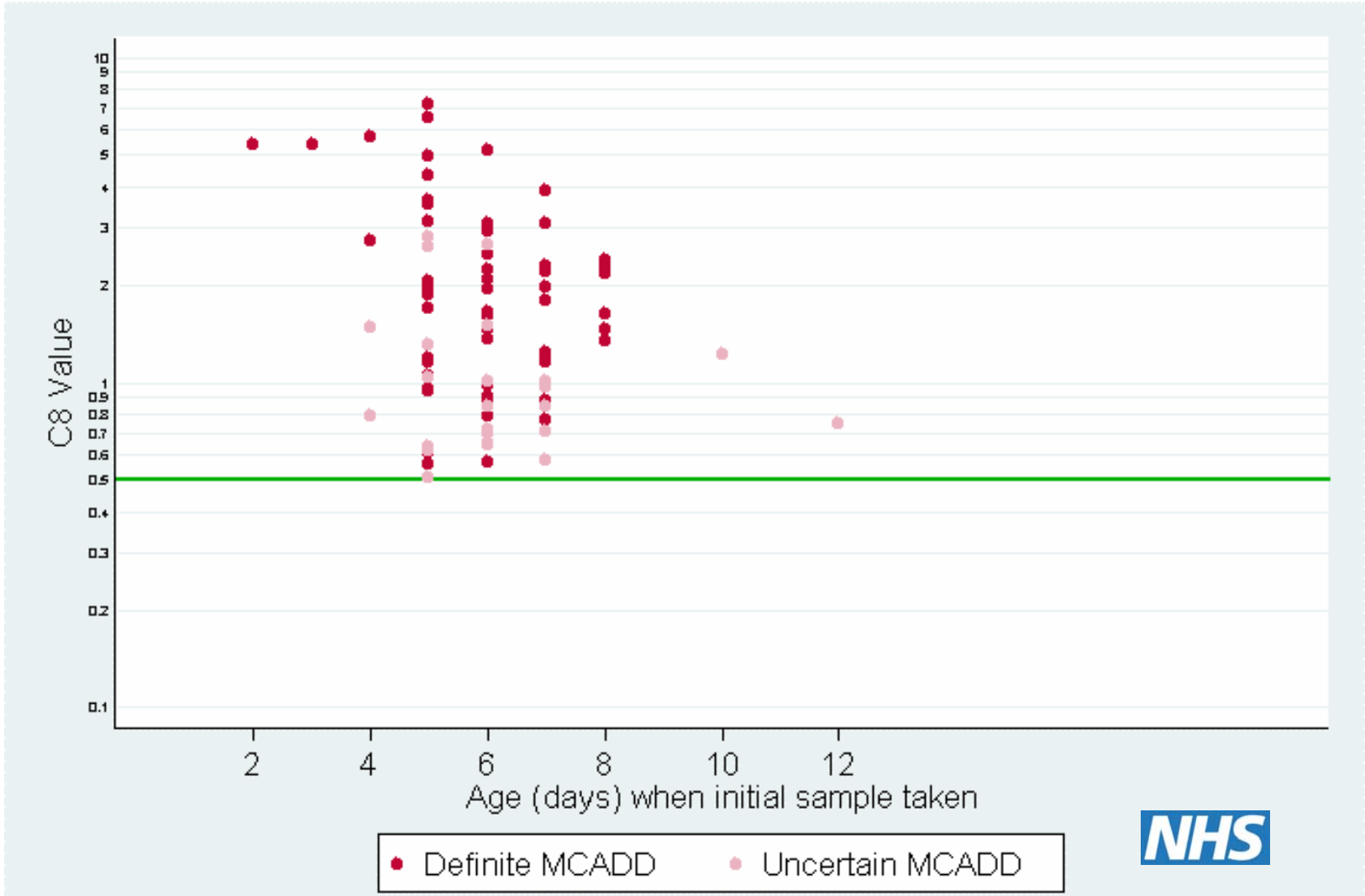
Following Independent Diagnostic Review of 103 completed cases:

MCADD	87
Definite phenotype	61
Uncertain phenotype	26
Carrier	11
Not Carrier/not MCADD	5

Contaminated card	1
Normal	1
Other Inborn error	3 (2 MADD, 1 unconfirmed)

UKCSNS MCADD

C8 by age at screening sample – All infants with MCADD



NHS

Positive Predictive Value (PPV) and Prevalence

N=103 (2 cases pending)

Definite MCADD Phenotype

PPV: 59% (61/103, 95% CI - 50%, 69%)

Prevalence ascertained by Screening:

61/745,387 = 0.8 per 10,000 (95% CI - 0.6, 1.0)

Definite and Uncertain MCADD Phenotypes combined

PPV: 84% (87/103, 95% CI - 78%, 91%)

Prevalence ascertained by Screening:

87/745,387 = 1.2 per 10,000 (95% CI – 0.9, 1.4)

Summary

- C8 performs well in the UK settting
  - Screen positive prevalence:
    ~ 1.4 per 10,000 live births
  - Based on strict definition of ‘definite’ MCADD phenotype
  - **Positive predictive value: 59%**
  - **MCADD prevalence ascertained by screening:**
    0.8 per 10,000 live births
  - Based on definition of ‘definite **and** uncertain’ MCADD phenotype
  - **Positive predictive value: 84%**
  - **MCADD prevalence ascertained by screening:**
    1.17 per 10,000 live births

- Quality measures
  - External QA scheme
  - QA group
  - Population data

Co-investigators & collaborators (6 centres)

Birmingham

Professor Anne Green, Dr Anupam Chakrapani, Dr Pippa Goddard, Dr Rachel Raynor, Dr Mary Anne Preece, Di Asplin

Sheffield

Dr Jim Bonham, Dr Melanie Downing, Professor Rodney Pollitt, Dr Simon Olpin, Dr Mark Sharrard

Leeds

Dr Mick Henderson, Dr John Walter, Dr Anthea Patterson

Manchester

Dr Guy Besley, Dr John Walter, Jackie Till

Guy's, London

Dr Neil Dalton, Dr Mike Champion, Dr Charles Turner, Dr Fiona Carragher

GOS, London

Dr Ying Foo, Dr Maureen Cleary, Dr Steve Krywawych

Co-investigators & Groups

Centre for Paediatric Epidemiology at the Institute of Child Health

- Carol Dezateux (PI), Juliet Oerton, Pamela Phillips, Bianca Stanford, Tim Cole

Diagnostic Review Panel:

- James Leonard (Chair), Jacqui Calvin, Morteza Pourfarzam, Graham Shortland, Johannes Zschocke

UK Newborn Screening Laboratory Network

– Don Bradley

British Inherited Metabolic Disease Group

- Graham Shortland, Marjorie Dixon

British Paediatric Surveillance Unit

– Richard Lynn, Jennifer Ellinghaus

Children Living with Inherited Metabolic Diseases

– Steve Hannigan, Pam Davies

UK Newborn Screening Programme Centre

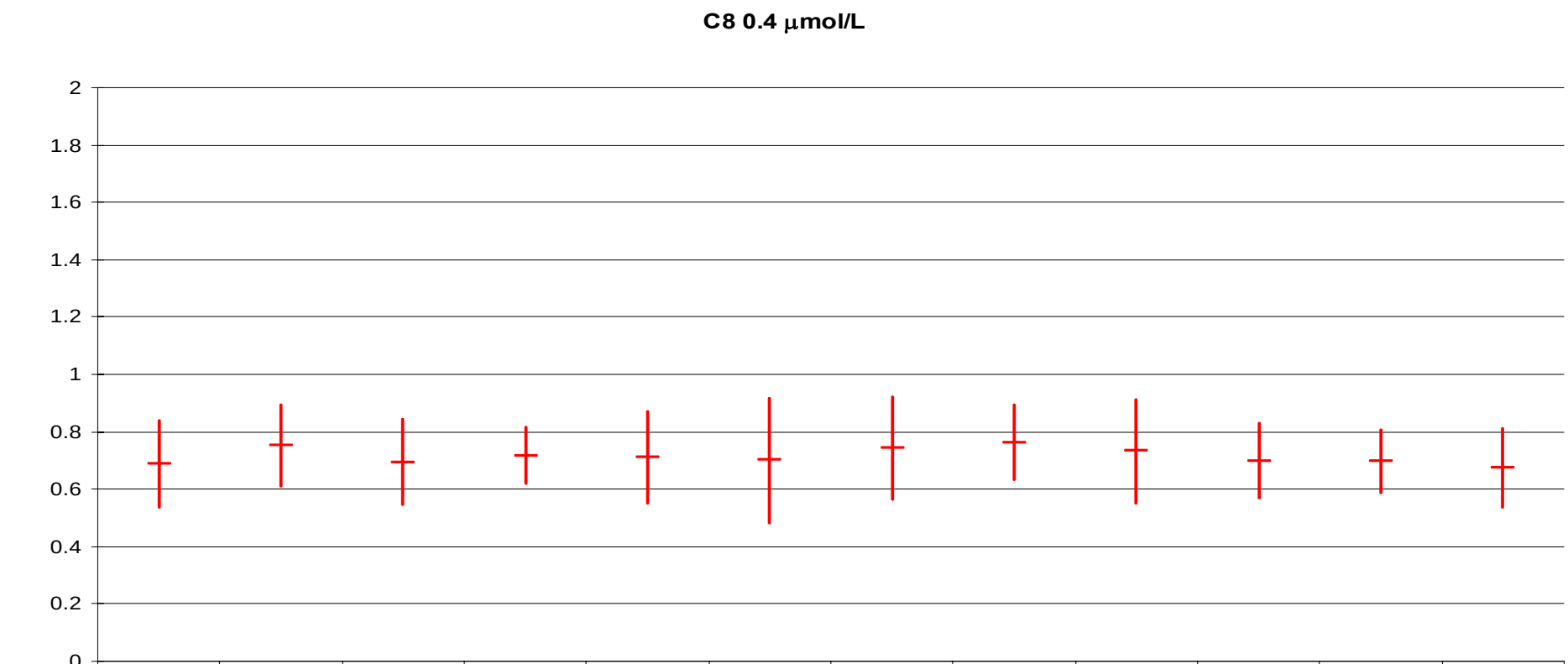
- David Elliman, Barbara Judge

Institute of Health Sciences, Aarhus, Denmark

- Brage Andresen

UKCSNS
MCADD

Mean of 6 Labs
+/- 2 SD



	1	2	3	4	5	6	7	8	9	10	11	12
upper	0.8372212	0.8957782	0.8429635	0.8158548	0.8715217	0.9175505	0.9222645	0.8949877	0.9139867	0.8298394	0.8057478	0.8117572
lower	0.5361121	0.6122218	0.5462032	0.6183119	0.5518117	0.4832828	0.5660688	0.6308456	0.5493467	0.5684939	0.5884188	0.5374095
– Mean	0.6866667	0.754	0.6945833	0.7170833	0.7116667	0.7004167	0.7441667	0.7629167	0.7316667	0.6991667	0.6970833	0.6745833

Quality Assessment of 985G>A

- Analysis of the common 985A>G mutation across four centres
  - **organised by the DNA Lab, Clinical Chemistry Department, Birmingham Children's Hospital.**

- Sample type and source
  - **surplus blood spots from known homozygotes and heterozygotes for the mutation and from normal controls, anonymised**
  - **blood spots distributed on National newborn screening cards.**
  - **quarterly distribution (4 specimens per distribution)**

Summary DNA EQA

- 6 distributions circulated
- 24 specimens
  - 2 failed analyses – different labs and different samples (early distributions)
  - 1 incorrect result (due to reporting not analytical error)

- From April 2005 Dr Andresen has been included in DNA EQA scheme for 985G>A
- 10 anonymous samples (to include heterozygous + homozygous for 985A>G and other disease causing mutations) have been assessed
  - All correct