Neonatal screening – progress, controversies and the impact of the BPSU

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Outline

• BPSU contribution to newborn screening for rare diseases

• Impact of BPSU studies – information about
  – Population burden of disease
  – Clinical service provision
  – Screening programme effectiveness

• Future challenges
  – Understanding long-term health and wider outcomes
BPSU surveillance for rare conditions

The BPSU “provides a simple and effective way of studying rare childhood disorders across the country. It allows the frequency of very rare diseases to be estimated reliably

... and the experiences of children and families ... before and after diagnosis to be understood.”

Sir Liam Donaldson, Annual Report of the Chief Medical Officer, 2009

Consequences of late diagnosis of a rare disorder

Source: European Organisation for Rare Diseases (Eurordis), 2005
Population screening

Systematic use of a test in a healthy population to identify individuals at high risk of a specific condition, for whom preventive action or effective early treatment would lead to improved health outcomes

Disease burden
- What is the condition? How common is it? How severe is it? What is the natural history? What are its consequences?

Clinical validity
- Can screening accurately identify those with the condition, without falsely labelling those without the condition?

Clinical utility
- Does the screening programme lead to an improved clinical outcome?

Unintended Consequences
- What is the impact of false positive and false negative screening results? Does screening lead to inequity in service provision?
Newborn & antenatal screening

**Metabolic/endocrine/Hb disorders**
- PKU & CHT
- Cystic fibrosis
- Sickle cell disorders
- MCADD
- Sickle cell and thalassaemia (antenatal)
- Glutaric aciduria type 1 & other inborn errors

**Congenital anomalies**
- Fetal anomalies (antenatal)
- Congenital cataracts
- Developmental hip dysplasia
- Congenital heart defects
- Sensorineural hearing loss
- Undescended testes
- Biliary atresia

**Congenital adrenal hyperplasia**
**Fetomaternal Alloimmune Thrombocytopenia**
**Galactosaemia**

**Other recessively inherited disorders**
- Duchenne muscular dystrophy (Wales)
- Severe combined immune deficiency

**Infections**
- HIV infection (antenatal)
- Rubella susceptibility (antenatal)
- Congenital syphilis (antenatal)
- Neonatal herpes
- Congenital toxoplasmosis
- Hepatitis C
- Congenital CMV
- Group B streptococcal disease

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Congenital Adrenal Hyperplasia (CAH): BPSU surveillance 2007-2009

- UK Newborn Blood Spot Screening Programme does not include CAH
- Uncertainty about incidence and disease burden

![Map showing incidence rates across the UK](image-url)
Burden of disease

**Birth prevalence:** 5.5 per 100,000 live births (1 in 18,248 births)

**Boys:** 43% (95% CI 35-51%)

- Boys remain undiagnosed for a longer period
  - under 50% boys recognised by Day 14 compared with 90% of girls
Screening for MCADD: BPSU studies

- MCADD: medium chain acyl dehydrogenase deficiency
- Recessive: over 80% clinical cases due to one gene mutation

Symptoms and signs
- Progressive metabolic crisis and collapse with fasting (vomiting, infection or surgery)
- Clinically and biochemically normal between episodes

Burden of clinical disease: 1994-96
- UK prevalence of clinically diagnosed MCADD: 0.5/10,000
- Significant mortality: ~28%
- 10% survivors had neurological impairment

Pollitt & Leonard 1998
UKCSNS-MCADD: pilot screening study

Unanswered questions

- Does screening detect *clinically relevant* MCADD?
- Does screening *prevent adverse clinical outcomes*?

MCADD pilot: BPSU 2004-2008

- 6 screening centres - 1.5 million infants screened
- Followed up at 1 and 2 years for:
  - Illness episodes & neurodevelopment

Key findings:

- Prevalence: 1 in 10,000 births
- High *clinical validity* – 70% confirmed cases had high likelihood of clinical presentation
- High *clinical utility* – MCADD screening effective in preventing adverse outcomes such as crises and deaths

Dezateux et al, 2004
Additional findings

Service provision
• 50% families had to travel 40km or further to access specialist services

Investigating the genotype using the newborn bloodspot
• most common gene mutation (c.985A>G homozygous MCADD) found in White but rarely in Black/Asian newborns

Investigating biomarker cut-off levels
• MCADD study data was used in a wider investigation of the appropriate cut-off levels for the screening biomarker on the blood spot
Congenital Hypothyroidism (CHT): BPSU study 2011-2016

• Prior to newborn screening:
  – Clinically presenting CHT: 1.5 in 10,000 births
  – More often affecting girls than boys (2:1)

• Newborn screening for CHT has been established for 30 years in UK

• BPSU surveillance:
  – To describe contemporary incidence in screened population
  – To describe outcomes at 3 years after diagnosis
  – To evaluate performance of newborn screening programme
Referrals by laboratory

- **Variation** in the number of **screen positive referrals** by laboratory:
  - Different cut-offs used by each laboratory
  - Population covered varies in size and characteristics

![Referrals by Laboratory Chart](chart.png)

- **Number of children referred after a positive screen result**

![TSH test cut-off during study shown in mU/L](chart.png)
Long-term follow-up

• Registers with consent (not all patients will consent)
  – Allow follow-up long-term with re-contact
  – Support studies involving patient-reported outcomes
  – Facilitate studies of clinical interventions
  – BPSU raises awareness of existing registers

• Record linkage – consent or unconsented (if privacy protected)
  – Potential to link to wider outcomes e.g. education, employment datasets
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