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Neonatal screening for sickle cell disease (Review)

Lees C, Davies SC, Dezateux C

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[Intervention Review]

Neonatal screening for sickle cell disease

Catherine Lees[1], Sally C Davies[2], Carol Dezateux[3]

[1]Paediatric Unit, Ward 20, Wishaw General Hospital, Wishaw, UK. [2]Standards & Quality Business Group, Research & Development Division, Dept of Health, London, UK. [3]Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London, UK

Contact address: Catherine Lees, Paediatric Unit, Ward 20, Wishaw General Hospital, 50 Netherton St, Wishaw, Scotland, ML2 0DP, UK. Catherine.Lees@lanarkshire.scot.nhs.uk.

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ABSTRACT

Background

Sickle cell disease is an inherited disorder that occurs throughout the world with its highest incidence in areas of Africa where malaria is endemic. It affects up to 1 in 60 infants born in some areas of Africa. There are a number of potentially serious complications associated with the condition, and it is suggested that early treatment (before symptoms develop) can improve both morbidity and mortality. Screening for the condition in the neonatal period would enable early diagnosis and therefore early treatment.

Objectives

To assess whether there is evidence that neonatal screening for sickle cell disease rather than symptomatic diagnosis reduces adverse short- and long-term outcomes for those in whom the disease is detected, without adverse outcomes in the population screened.

Search methods

We searched the Haemoglobinopathies Trials Register of the Cochrane Cystic Fibrosis and Genetic Disorders Group. Contact was made with experts in the field for any work as yet unpublished. Reference lists of published studies were also searched.

Date of the most recent search of the Group's Trials Register: 09 April 2010.

Selection criteria

Any randomised or quasi-randomised trial, published or unpublished comparing diagnosis by screening to clinical diagnosis would have been considered eligible for inclusion.

Data collection and analysis

No trials of neonatal screening for sickle cell disease were found.

Main results

No trials of neonatal screening for sickle cell disease were found.

Authors' conclusions

There is a lack of evidence from trials of neonatal screening for sickle cell disease.

There is evidence of benefit from early treatment which is made possible by screening and there are a number of reviews and economic analyses of non-trial literature suggesting that screening is appropriate. Healthcare providers must therefore assess whether the

information provided by these documents is relevant to their practice and situation when making decisions regarding neonatal screening for sickle cell disease.

Systematic reviews of early treatments or interventions, including penicillin prophylaxis, pneumococcal vaccine and parental education should be considered.

There are no trials included in the review and we have not identified any relevant trials up to July 2008. We therefore do not plan to update this review until new trials are published.

PLAIN LANGUAGE SUMMARY

Testing newborn babies for sickle cell diseases

Sickle cell diseases are inherited and affect mainly people of African origin. The red blood cells are abnormally (sickle) shaped, which can lead to life-threatening complications. They are most likely to be fatal in the first few years of life since affected children are at higher risk of serious infections. Regular antibiotics and immunisations reduce the risk of infections, and if sickle status is known, can be started early. Screening babies allows early diagnosis and therefore early treatment. Screening may also have disadvantages. This review aims to assess whether screening compared to diagnosis from symptoms leads to less morbidity and mortality. The authors were not able to find trials that assessed the benefits and harms of screening. There is evidence that starting treatment early is of benefit. Early treatment is made possible by screening in the neonatal period. There are some reports in non-trial literature which suggest that newborn screening is appropriate based on currently available evidence. Healthcare providers must assess whether these reports are relevant to their practice and situation when deciding whether to screen for SCD in the neonatal period. Practice recommendations could be made from the results of a prospective randomised controlled trial. Such a trial may be thought to be unethical given the proven benefit of early preventative treatment of children with penicillin. There are no trials included in the review and we have not identified any relevant trials up to July 2008. We therefore do not plan to update this review until new trials are published.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a group of inherited conditions of red blood cells affecting mainly individuals of African origin but also Indian, Saudi and some Mediterranean populations. The gene is widely distributed with carrier prevalence ranging from 1% to 40% of the different populations at risk and the highest frequencies occurring in Africa where the incidence of sickle cell anaemia varies from 1 to 3 per 1000 to 1 in 60 black infants born (Granda 1991; Serjeant 1994).

The conditions are characterised by abnormal (sickle) shaped red blood cells caused by an abnormality in the structure of the haemoglobin molecule within the cell. This results in the red cells being removed prematurely from the circulation (haemolysis).

The shape of the haemoglobin molecule is programmed by a pair of genes (alleles) which individuals inherit from their parents (one gene from each parent). There are a number of different forms of these genes and therefore a variety of combinations of genes that may be inherited by any individual. This results in a number of sickle cell diseases including sickle cell anaemia (SS), sickle-haemoglobin C disease (SC), Sß thalassaemia (two different forms: Sβ0 and Sβ+), sickle cell haemoglobin D disease (SD) and sickle cell haemoglobin E disease (SE). Of these, SS, SD and Sβ0 are more severe with Sβ+ and some forms of SC tending to be milder. Each condition however may result in similar problems and complications, some of which are severe and potentially life threatening.

A few people with SCD are asymptomatic, with little or no interruption to their daily life. All children with SS and Sβ however, become anaemic in the first year of life.

The highest mortality occurs in the first five years of life (reported variously as 2% to 30%) (Overturf 1977; Serjeant 1994; Vichinsky 1988), although more specifically in the second six months (Rogers 1978). The most severe and potentially life-threatening complications in this age group include infection, splenic sequestration and aplastic crises that result in a severe anaemia of rapid onset. However, SCD confers some degree of protection against the morbidity and mortality associated with malarial infections, which is of particular relevance in developing countries where the highest incidences of both SCD and malaria are found.

Other problems associated with SCD include acute chest syndrome (a condition of varying severity comprising a range of features including new infiltrate on chest X-ray combined with fever, respiratory symptoms or chest pain); central nervous system (CNS) events including strokes; and painful crises (bone and abdominal).

People with SCD have an increased susceptibility to severe bacterial infections (particularly pneumonia, meningitis and osteomyelitis) with a 20% incidence of sepsis reported in infants under one year and a reported mortality rate of up to 35% (Topley 1981). The incidence of splenic sequestration episodes (rapid worsening of anaemia because a large quantity of blood is collected in the spleen also causing splenic enlargement) is reported at up to 25% (Topley 1981). Overall, up to 15% of the reported childhood mortality in SCD is due to sepsis or sequestration crises (Powars 1981).

More chronic problems include multi-organ damage associated with acute and chronic vaso-occlusion (obstruction of small blood vessels), gall bladder disease, delayed growth and onset of puberty (Stevens 1986), avascular necrosis of bone (i.e. destruction of areas of bone caused by a disturbance to the blood supply to the bone). There is also a potential for psychosocial and emotional problems particularly in areas where the conditions are less common.

There are two main components to the treatment of SCD, preventative and supportive. People with SCD are particularly susceptible to infections with encapsulated organisms (particularly Pneumococcus, Salmonella species, Meningococcus and Haemophilus). Preventative treatments therefore include administration of regular prophylactic penicillin, immunisation (against both Pneumococcus and Haemophilus) and education (regarding avoidance of factors that might cause illness and early recognition of the signs of illness) and support for parents caring for these children. Supportive therapies include treatment of acute episodes with fluid therapy, pain relief, blood transfusion and other measures depending on the severity of such episodes and the treatment of the more chronic problems. Bone marrow transplantation, a potentially curative treatment, is also now available. This is, however, a relatively new treatment and is still being evaluated.

The administration of penicillin from an early age (four months) to prevent infection with Pneumococcus has been shown to reduce the incidence of pneumococcal infections by 84% (an absolute risk reduction of 10%), and reduce mortality from such infections in children with SCD (Gaston 1986). There is, however, debate about the appropriate age at which treatment should stop. Also, the incidence of penicillin-resistant Pneumococcus varies worldwide, and there is debate about how effective this treatment is in areas with a high incidence of resistance.

The high mortality in the first year of life, and the potential to reduce this through early administration of penicillin prophylaxis and education of parents in recognising the early signs of potentially serious complications such as splenic sequestration suggests that early diagnosis of SCD could reduce morbidity and mortality. This is particularly relevant in the more severe forms of the disease. Early diagnosis would also enable education of parents and families about the condition. One method by which early diagnosis could be achieved is screening.

Description of the intervention

Neonatal screening would provide not only a method of early detection for people with SCD, but also enable detection of another group - those with sickle cell trait (carrier status) (AS). These individuals are healthy and asymptomatic, and the implications of detection of this state are related principally to future reproductive risks.

Screening may be offered at a number of stages of a person's life and the neonatal period is one of these. The reported advantages of early diagnosis in SCD suggest that neonatal screening may be helpful in achieving this.

How the intervention might work

Screening programmes provide many potential advantages, but there is also the risk of harm. Wilson and Jungner proposed criteria

to be met before screening programmes are implemented (Wilson 1968). These have been revised for use in the UK (DoH 1998) and the Netherlands (HCNI 1994). There are a number of possible methods for neonatal screening for SCD. Sampling may be done on a universal (all neonates) or selective (high-risk infants) basis. Cord blood, routine dried blood spot, or capillary heelprick samples may be used, and there are a number of laboratory methods available for identifying the abnormal haemoglobin molecules that characterise SCD (AHCPR 1993; Lorey 1994).

The result of a screening test done in the neonatal period for any inherited disorder has immediate implications for the infant found to have the condition, but also longer-term implications for both the child and other family members. Parents and other family members need education regarding the condition and care of the infant and also support and information regarding the genetic implications. To this end it is important that a screening programme provides early, reliable diagnosis and communication of the results. This then enables initiation of appropriate treatment if available, and also support for the family in the educational aspects of the condition and regarding the genetic implications for those with SCD, and those found to be carriers.

As with screening for other conditions, there are potential adverse effects of screening for SCD. False positive results (screening test reported positive when the child does not have the condition) will cause unnecessary parental anxiety. Conversely, false negatives (the screening test reported negative when the child actually does have the condition) could result in serious illness or infant death or both. A further complication in SCD is that carrier status (AS) will also be detected through neonatal screening. This has no immediate medical implications, but becomes relevant when considering future reproductive plans. Carrier status does however confer a degree of protection from malaria. There is some evidence from adult screening studies that informing carriers of positive aspects of a screening result is important (Karetti 2004).

Delay in communicating results causes not only an anxious wait, but also a delay in commencing treatment and possibly failure to recognise serious complications due to lack of knowledge.

Why it is important to do this review

This review aims to assess whether neonatal screening for SCD as opposed to symptomatic diagnosis contributes to a reduction in morbidity or mortality or both from the condition.

OBJECTIVES

The purpose of this review was to assess whether neonatal screening for SCD (rather than symptomatic diagnosis) reduces short- and long-term adverse outcomes for those in whom the disease is detected, without adverse effects in the population screened.

In this review the term SCD refers to the more common forms of the group of disorders described previously that are characterised by the presence of abnormal haemoglobin molecules. This includes sickle cell anaemia (SS) (the most common), SC, Sβ0 and Sβ+, SD and SE.

We aimed to address the following:

1. Is screening for SCD effective at reducing the mortality and morbidity in children who have the condition?
2. Does screening for SCD cause adverse effects in the population screened?

Issues regarding the actual laboratory diagnostic tests employed were not considered.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-randomised controlled trials, both published and unpublished.

Types of participants

All children screened for SCD and all children diagnosed with SCD.

Types of interventions

All neonatal screening programmes enabling early pre-symptomatic diagnosis of SCD. Trials where screening infants for SCD has been compared to not screening were considered for inclusion. Trials where historical or concurrent controls were used, and those that reported the performance of diagnostic tests were not included.

Types of outcome measures

For the purposes of this review, a false positive result is where a child is identified by a screening test as having SCD when they do not. A false negative result means that after a screening test, a child is said not to have SCD when they do in fact have the condition.

We wished to address the outcome measures listed below in the first five years of life in the group diagnosed with SCD.

Primary outcomes

1. Death from the disease or its complications
2. Hospital admissions resulting from the disease or its complications
3. Incidence of complications or conditions resulting from a SCD not requiring hospital admission
4. Growth of children with sickle cell disease

Secondary outcomes

1. All adverse effects (including psychological and effects on family relationships) resulting from the diagnosis of sickle cell disease
2. All adverse effects including delayed diagnosis of SCD, resulting from a false negative result
3. All adverse effects resulting from difficulties in communicating results (either positive or negative)
4. Measures of quality of life

We wished to assess the outcomes listed below in the screened population.

Primary outcomes

1. Adverse effects in the screened population including psychological damage such as anxiety or guilt following false

positive tests, interference with developing family relationships and misconceptions and miscommunication of results
2. All effects of a diagnosis of the carrier state including psychological damage, interference with developing family relationships, and misconceptions and miscommunications of the results
3. All effects of false negative or false positive diagnosis of the carrier state (see methods section)
4. The direct medical costs of screening for SCD

Secondary outcome

1. The opportunity to make reproductive choices when knowledge of an individual's sickle cell status (i.e. being a carrier or having a sickle cell condition) is available

We planned to group outcome data into those measured at one, three, six and twelve months and annually thereafter for five years. Data recorded at other time periods would also have been considered.

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND screening.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 09 April 2010.

Searching other resources

The bibliographic references of all retrieved studies and reviews were to be assessed for additional reports of trials and contact was made with experts in the field for any work as yet unpublished.

Data collection and analysis

For the purpose of this review, the following definitions were used:

- false positive test result: a child is identified by the screening test as having SCD when they do not;
- false negative test result: a child has a negative screening test when they actually do have SCD;
- false positive carrier state: a child is identified by the screening test as carrying the sickle cell trait (AS) when they do not;
- false negative carrier state: a child is not detected by the screening test as having the sickle cell trait (AS) when they actually do

There are currently no studies included in this review. If we are able to include studies in a future update, we plan to conduct the following.

Selection of studies

We plan to independently select trials for inclusion in the review. We will resolve any disagreement through discussion.

Data extraction and management

We plan to independently extract data from the included trials using a specifically designed data extraction form . We will resolve any disagreement through discussion.

Assessment of risk of bias in included studies

We plan to independently assess the risk of bias in the included studies by assessing the methodological quality of these using a modification of the method described by Schulz (Schulz 1995). We plan to include the following in our assessment: allocation concealment; generation of the randomisation sequence; whether assessment of outcomes was blinded; whether intention-to-screen analyses were possible from the available data; and if all participants were accounted for at the end of the study.

Measures of treatment effect

For binary outcome measures, to allow an intention-to-screen analysis, we will seek data on the number of participants with each outcome event, by allocated screened group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from the programme or follow up. For these outcomes, we will calculate a pooled estimate of the treatment effect for each outcome across studies (the odds of an outcome among treatment-allocated participants to the corresponding outcomes among controls).

For continuous outcomes, we will record either the mean change from baseline for each group or mean post treatment or intervention values and standard deviation or error for each group. Also, we will calculate a pooled estimate of treatment effect by calculating the weighted mean difference.

Dealing with missing data

We will request further information from the studies' primary investigators where required.

Assessment of heterogeneity

We plan to test for heterogeneity between trial results using a standard chi-squared test.

Assessment of reporting biases

If possible, we will assess publication bias using a funnel plot. We will try and identify and report on any selective reporting in the included trials.

Data synthesis

If we are able to enter data in a meta-analysis, we plan to use a fixed-effect model. If we feel there is statistical heterogeneity between studies, we will use a random-effects model.

Sensitivity analysis

We will perform a sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomised studies.

RESULTS

Description of studies

No studies were found that were eligible for inclusion in the review.

Risk of bias in included studies

No studies were included in the review.

Effects of interventions

No studies were eligible for inclusion in the review.

See Discussion.

DISCUSSION

SCD occurs throughout the world with the highest incidence in people originating from areas in Africa where malaria is endemic. It also affects individuals of Indian, Saudi and Mediterranean extraction. The highest incidence occurs in Africa (on average 1 to 3 per 1000 black infants born although up to 1 in 60 babies born in Nigeria), but increasing population migration has resulted in an increasing occurrence throughout the world. It affects an estimated 50,000 in North America (AHCPR 1993) and it was predicted that by the year 2000 more than 10,000 people would be affected in the UK (Davies 2000).

At present, screening of neonates for SCD is carried out in a number of areas throughout the world, but the evidence used for establishing and appraising screening programmes has come mainly from observational studies. More recently however, it has been suggested that the optimum study design for assessing both performance and viability of screening is either a systematic review of RCTs, or a well-conducted RCT (Muir Gray 1997).

These study designs allow methodological issues that are particularly associated with screening interventions, specifically ascertainment and lead-time bias, to be addressed. These are defined in Last's dictionary of epidemiology as follows: Ascertainment bias is "a systematic error arising from the type of individuals or patients (mildly ill, moderately ill or severely ill) that the individual observer is seeing. Also systematic error arising from the diagnostic process". Lead-time bias is "a systematic error arising when follow up of two groups does not begin at strictly comparable times" (Last 1995).

This systematic review has highlighted a lack of prospective randomised controlled trials of neonatal screening for SCD. The practice of neonatal screening is however supported by evidence from observational studies as well as from a randomised trial of penicillin prophylaxis (Gaston 1986).

Neonatal screening allows early diagnosis and therefore early treatment and education. An RCT of prophylactic penicillin in a screened population has shown that prophylactic penicillin in sickle cell anaemia (SS) before symptoms develop reduces the incidence of and mortality from pneumococcal sepsis in children (Gaston 1986). There is also evidence to suggest that pneumococcal vaccine as well as parental education to recognise early signs of some of the life threatening complications of SCD lead to improved outcomes (Lee 1995).

In industrialised countries, there is considerable experience of using high performance liquid chromatography (HPLC) to test newborns for SCD using, when available, the dried blood spot collected from all newborns for phenylketonuria (PKU) and hypothyroidism screening. However, other laboratory techniques may be employed and several of these processes appear to be simple, safe, reliable and valid (AHCPR 1993; CTFPHC 1994; USPSTF 1996). These are all prerequisites for screening programmes (Wilson 1968).

Guidelines and reviews of screening programmes have been published by a number of agencies internationally. These include US Department of Health and Human Services which supports universal screening of all neonates (AHCPR 1993) and the US Preventive Services Task Force which suggests that the screening strategy (universal or selective) should depend on the proportion of high-risk individuals in a community (USPSTF 1996). A recent cost-effectiveness analysis is supportive of targeted neonatal screening, and suggests that universal screening is worthwhile in certain situations (Panepinto 2000). However, experience in the USA suggests that effective targeting strategies are difficult to define and the criteria used to identify ethnic origin in relation to risk of sickle carrier status are likely to vary between and within countries making the generalisability of such analyses difficult to interpret. The Canadian Task Force on Preventive Health Care document suggests that neonatal screening should be performed on high-risk infants, and also provides grading of each recommendation based on the level of evidence used (CTFPHC 1994). The World Health Organisation has also produced a guideline document which provides planning guidelines for screening programmes, and recommendations for screening practices in different areas (WHO 1994). In the UK, two reviews on economic evaluation and cost modelling of screening for haemoglobinopathies commissioned by the Health Technology Assessment programme have been published (Davies 2000; Zeuner 1999). These suggest that neonatal screening is worthwhile even in the context of universal or selective antenatal screening programmes. The National Plan for the NHS announced the development of a linked antenatal and neonatal screening programme for England (DoH 2000).

AUTHORS' CONCLUSIONS

Implications for practice

No RCTs of screening were found for inclusion in this review.

There is, however, evidence of benefit from early commencement of treatment in SCD, which is made possible by screening in the neonatal period. There are also a number of reviews and economic analyses of non-trial literature suggesting that newborn screening is appropriate based on currently available evidence.

Healthcare providers must therefore assess whether the information contained in these documents is relevant to their practice and situation when making decisions regarding neonatal screening for SCD.

There are no trials included in the review and we have not identified any relevant trials up to July 2008. We therefore do not plan to update this review until new trials are published.

Implications for research

Information from a well-designed prospective RCT of neonatal screening is desirable in order to make recommendations for practice. However such trials may now be considered unethical in view of the proven benefit of early prophylactic treatment with penicillin.

As treatment effectiveness is central to the rationale for newborn screening, and given the high sensitivity and specificity of available tests, systematic reviews of early treatment including prophylactic penicillin, pneumococcal vaccine and parental education should be considered.

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Dr M. Bhavnani, Consultant Haematologist, Wigan
Professor B. Modell, Department of Primary Care and Population Sciences, University College London
Professor J.P. Neilson, Department of Obstetrics and Gynaecology, University of Liverpool, Co-ordinating Editor Cochrane Pregnancy and Childbirth Group
Dr J. Wright, Consultant Haematologist, Sheffield
Dr L. Styles, Haematology/Oncology Department, Children's Hospital, Oakland, California.

We thank Dr A. Olujohungbe, Liverpool, for providing consumer comments.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bardakjian 2000	It was unclear from the report how participants were recruited.
Modell 1998	This study did not address the relevant intervention (neonatal screening) or target population (newborns).

APPENDICES

Appendix 1. Comment & Criticism (published Issue 3, 2001)

Neonatal screening for sickle cell disease

Summary

I noted a few things about this review while preparing an abstract for the journal Evidence-based Health Care.

1. There is some discrepancy between your summary, the body of the text and the stated methods for the review group about exactly what the search strategy was.

2. I think you need to say something in the summary about whether the absence of trial evidence is important.

3. One of the very valuable components of the review is to point to other evidence and summaries of non-RCT data which might help with decisions on this intervention in the absence of trial data. Could you indicate in the abstract that refs to these are available in the main text of the review. Further, do you think it might be useful as part of the review to formally appraise these and indicate which if any provide reliable summaries of the non-RCT evidence?

Hope these comments are of assistance.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Thank you for your interest in our review, and taking time to comment.

Our response is:
1. The search strategy used for the review was that described in the group's procedures. Additional attempts to find randomised controlled trials (RCTs) were made through contact with experts in the field, and the reference lists of studies. There are differences in the expression of this in the abstract and the methods section. We will clarify this in future updates of the review.

2. We have made comment on the lack of trial evidence in the 'Implications for Practice' and 'Implications for Research' sections of the review. However, evidence from trials that penicillin prophylaxis in infants diagnosed early results in a significant reduction in mortality, suggests that future trials of screening may be considered unethical or not feasible. While screening programmes should ideally be based on evidence from RCTs, there are a number of instances (e.g. neonatal screening for PKU) where this is not the case.

3. We plan not to indicate in the abstract that there are references to non-RCT data within the main text of the review. We acknowledge that there are other methods of evidence synthesis that can make use of non-RCT data and these have been used in two recent UK Health Technology Assessment reports that have been published (1,2).

1. Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. Health Technology Assessment. 1999;3(11):i-v, 1-186.

2. Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. Health Technology Assessment. 2000;4(3):i-v, 1-99).

We would wish to affirm that RCT and non-RCT data can provide useful information when assessing the performance, effectiveness and efficiency of screening and of different screening strategies, none of which can be addressed by a meta-analysis of RCTs which are generally concerned with a single intervention rather than screening and a treatment pathway. These issues have recently been discussed in a commentary by Royston in the British Medical Journal (Royston G. Commentary: trials versus models in appraising screening programmes. British Medical Journal. 1999 Feb 6;318(7180):360-1).

Contributors

Comment received from: Dr Chris Hyde, December 2000
Reply from: Dr Catherine Lees, Professor Sally Davies, Dr Carol Dezateux, June 2001

WHAT'S NEW

Date	Event	Description
16 April 2010	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials eligible for inclusion in the review.
16 April 2010	Review declared as stable	There are no trials included in the review to April 2010. We therefore do not plan to update this review until new trials are published, although we will search the Grouup's Haemoglo-binopathies Trials Register on a two-yearly cycle.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 1, 2000

Date	Event	Description
13 August 2008	Review declared as stable	There are no trials included in the review up to July 2008. We therefore do not plan to update this review until new trials

Date	Event	Description
		are published, although we will search the Group's Haemoglobinopathies Trials Register on a two-yearly cycle.
13 August 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identiify any trials eligible for inclusion in the review.
15 April 2008	Amended	Converted to new review format. A new plain language summary has been written in line with latest guidance from The Cochrane Collaboration.
15 April 2008	New search has been performed	The search of the Group's Haemoglobinopathies Trials Register did not identify any new references for this review.
22 August 2007	Amended	The 'Background' section of the review has been amended and includes a new reference (Karetti 2004).
22 August 2007	New search has been performed	No eligible trials were identified from the search of the Group's Haemoglobinopathies Trials Register.
31 January 2006	New search has been performed	The search of the Group's Haemoglobinopathies Trials Register did not identify any new references for this review.
28 January 2005	New search has been performed	The search of the Group's Haemoglobinopathies Trials Register identified one trial which was not eligible for inclusion in the review.
21 January 2004	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not find any trials eligible for inclusion in the review.
16 December 2002	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not find any trials eligible for inclusion in the review.
22 October 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Catherine Lees wrote the text of the review and acts as the guarantor of the review.

Sally Davies and Carol Dezateux provided expert opinion and advice on haemoglobinopathies and screening, and commented on the protocol, the final review and the updated reviews.

DECLARATIONS OF INTEREST

None known.

NOTES

A 'Comment and Criticism' entitled: 'Neonatal screening for sickle cell disease' (and the response from the reviewers) was attached to this review on Issue 3, 2001. This now appears as an appendix to this review (Appendix 1).

INDEX TERMS

Medical Subject Headings (MeSH)

*Neonatal Screening; Anemia, Sickle Cell [*diagnosis]

MeSH check words

Humans; Infant, Newborn