UK National Screening Committee

Screening for iron deficiency anaemia in children under 5 years of age

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Introduction

Iron deficiency anaemia

Iron has several vital functions in the human body. Too little iron can lead to morbidity and mortality.

Infants and children aged less than 24 months, particularly those aged between 9 and 18 months are at the highest risk of any age group of developing iron deficiency (ID). This is due to a rapid rate of growth which is often accompanied by an inadequate intake of dietary iron.

Iron status is a continuum. Iron deficiency anaemia (IDA) occurs when ID is severe enough to affect red blood cell production, and to cause haemoglobin (Hb) concentration in the blood to fall two standard deviations below the mean for a particular population.

IDA during infancy has been associated with several negative outcomes. In particular, it is thought to adversely affect psychomotor, cognitive and behavioural development.

Current policy

Screening for IDA in children less than 5 years of age is not current UK policy. The last review of this policy took place in 2006. No review document was produced at this time but the policy of not screening was reaffirmed along with the advice that the emphasis should be on primary prevention and good nutritional advice.

This report

This report uses evidence published from 2006 to 2011 to update the review of screening for IDA in children less than 5 years of age against the UK National Screening Committee (NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003).

To provide an indication of the evidence base available up to 2006, the report refers to the 2006 US Preventative Services Task Force (USPSTF) review of screening for IDA in children between 6 to 12 months of age where appropriate. This review concluded that there was insufficient evidence to recommend for or against routine screening for IDA in asymptomatic children aged 6 to 12 months.[1] To provide background information on what is known about IDA in the UK, publications from 1996, 1999 and 2001 containing results from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) are referred to where appropriate. This study examined Hb and ferritin concentrations in children aged 8 months, 12 months and 18 months in a random sample of children born during the last 6 months of 1992 in the Bristol and District Health Authority area.

It should be noted that there is a lack of consensus between US bodies over screening for IDA. The American Academy of Paediatrics (AAP) published a clinical report in 2010 which recommended universal screening for anaemia at approximately 12 months of age with determination of Hb concentration and assessment of risk factors associated with ID/IDA.[2] For infants and toddlers (1-3 years of age), additional screening can be performed at any time if there is a risk of ID/IDA.[2] The US Centers for Disease Control and Prevention (CDC) recommends periodic screening for IDA in high-risk infants and preschool children.[3] The USPSTF review states that the American Academy of Family Physicians (AAFP) recommends screening for IDA in high-risk infants aged 6 to 12 months and in infants whose principal dietary intake is unfortified cow's milk.[4]

The USPSTF were unable to determine the balance between the benefits and harms of routine screening for IDA in asymptomatic children aged 6 to 12 months.[4] The reasons for this centred on:

- Natural history. In many cases, particularly in children less than 12 months, ID and IDA resolve spontaneously. Furthermore a causal relationship between IDA and developmental abnormalities is difficult to establish.
- The test. The specificity of serum Hb assessment or haematocrit (Hct) was a concern as there are many causes of anaemia other than ID. The sensitivity and specificity of alternative methods, for example measurement of serum ferritin (SF) or transferrin saturation, has been insufficiently studied.
- The treatment. There was conflicting evidence that iron supplementation leads to improved outcomes.

This update report assesses new evidence in these areas, in a wider population of children less than 5 years of age, and comments on additional NSC criteria for screening.

For this report an updated systematic search has been performed for relevant publications from January 2000 to 4th January 2010. This search was repeated on 28th October 2011. Overall, 293 citations were judged to be relevant (see Methodology section for study breakdown).

This report focuses on publications since 2006, since this was the date of the last policy review. The full text of selected papers was retrieved after a first pass appraisal at abstract level. Additional relevant references identified during the preparation of the report were also included. An overview of the most informative and relevant references regarding the individual screening criteria is given below. Guidelines, systematic reviews and studies from the UK, Europe and the US were prioritised.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

1. The condition should be an important health problem

In this criterion evidence published since 2006 addressing morbidity associated with IDA was assessed. Prevalence of IDA is addressed in Criterion 2.

The USPSTF states in their 2006 summary of screening recommendations that *"iron deficiency is associated with psychomotor and cognitive abnormalities in children."*[4]

IDA has been associated with adverse effects on cognitive performance, motor development, behaviour and physical growth of infants and preschool aged children. In the AAP clinical report 2010 they concentrated on the effects of IDA on neurodevelopment.[2] They state that although an unequivocal relationship between IDA and neurodevelopmental outcomes has yet to be established, *"it is important to minimise IDA and ID among infants and toddlers*." They cited a 2001 Cochrane review which investigated whether iron therapy improved psychomotor development and cognitive function in children under three with IDA (edited in 2009)[5] and a 2007 narrative review by McCann and Ames.[6]

The 2007 narrative review by McCann and Ames was a review of expert opinion and major evidence for a causal relation between dietary ID during development and deficits in cognitive or behavioural function.[6] According to the review, studies have found consistent association between IDA and poor cognitive and behavioural test performance relative to controls in children <2 years of age. Additional reviews were cited that reported that children >2 years of age with IDA also often perform worse than control children, at least on some measures. However, McCann and Ames noted that a link between IDA and poor test performance is difficult to establish because of potential confounding by socioeconomic factors and by the presence of anaemia.[6] The major conclusions of this review were that:

"Although most of the 5 conditions for causality (association, plausible biological mechanisms, dose response, ability to manipulate the effect, and specificity of both cause and effect) are partially satisfied in humans, animals, or both, a causal connection has not clearly been established. In animals, deficits in motor activity are consistently associated with severe IDA, but adverse effects on performance in tests that target cognitive function have not been clearly shown. Resistance to iron treatment was observed in most trials of children <2 years of age with IDA, but not in older children. Similar observations were made in rodents when IDA occurred before rather than after weaning."

In addition to possible effects of IDA on cognitive and behavioural outcomes, there is also an interaction between iron and lead. The 2010 AAP clinical update cited three animal and human studies that have shown that IDA increases the intestinal wall absorption of lead, and one epidemiological study that found that IDA is associated with increased blood lead concentrations in children aged 9 to 48 months. In addition, the report cited studies that suggest that IDA affects the efficiency of lead chelation therapy. This is important due to the reported neurotoxicity due to even very low blood concentrations of lead.[2]

A number of other studies identified in the update search looked at the association between IDA and a number of outcomes. Publications from three large cohort studies performed in Chile, the US and Costa Rica were identified. Publications since 2006 are described below.

The Costa Rican study enrolled healthy children at 12 to 23 months of age and followed them up for 19 years. Iron status was determined, and all children except those with Hb ≥12.0g/dL and good iron measures were treated with iron. Anaemia resolved with treatment in all children with IDA. Children with good iron status either before or after treatment were compared to those who had chronic or severe ID in follow-up studies. Good iron status was defined as Hb ≥12.0g/L and no other abnormal iron measures. Chronic or severe ID was defined as Hb ≤10.0g/dL and two or more abnormal iron measures before therapy, or Hb>10.0g/L and ID which was not fully corrected after 3 months of iron therapy. At 5 years of age, children with chronic or severe ID at 12 to 23 months of age had impaired mother-child interaction. During a structured task, children with chronic or severe ID at 12 to 23 months of age were more likely to display lower levels of physical activity, positive affect, and verbalisation, and lower mother-child reciprocity was observed. Mothers of children with chronic ID showed less responsivity during the structured task in both a laboratory setting and during everyday interactions in the home.[7] In this study, the gender of the child was included as a covariate in all analyses. Five other demographic and family background variables were adjusted for when they were found to be covariates: child and mother age, father absence in the home, maternal education and maternal depression.[7]

Motor development was assessed before and after one week and three months of iron therapy, and then at 5 years and 11-14 years of age. Children in the chronic or severe ID group had lower motor scores at the start of the study. A lower but parallel trajectory of motor scores was observed over follow-up, with no evidence of catch-up.[8] A propensity score adjustment was used to control for gender, birth weight, infant feeding practices, age at enrolment, family structure, socioeconomic status, mother's IQ and quality of the home environment. The final model was adjusted for gender, growth, pubertal status and propensity score.[8]

At 19 years of age, individuals who had chronic or severe ID performed less well on frontostriatal-mediated executive functions, including inhibitory control, set-shifting and planning, and exhibited impairment on a hippocampus-based recognition memory task.[9] Background variables were considered as potential covariates (age; birth weight; gender; if the infant was breastfed; age of weaning; amount of milk or formula per day; age of introduction of cow's milk; number of bottles per day; mother's education; mother's IQ; whether the father was present; whether grandparents were present; quality of the home environment; socioeconomic status; participant IQ), and included as covariates if they were found to correlate with results of a specific test.

There was also a "*double burden of iron deficiency in infancy and low socio-economic status*." In participants of middle socioeconomic status the difference between the cognitive scores of children who had severe or chronic ID at 12 to 23 months of age and those with good iron status remained at 8 to 9 points at 19 years of age, similar to the difference at enrolment. However, in participants of low socioeconomic status, the gap widened from 10 points at enrolment to 25 points.[10] Socioeconomic status was assessed using the Hollingshead Four Factor Index, which considers parental education and occupation, and father's presence. Gender and birth weight were covaried in all analyses.[10]

Two publications relating to the Chile cohort were identified. One was a RCT which investigated the utility of a home intervention in combination with iron therapy and will be discussed in criterion 10. However, it is relevant to note that while at the start of the trial infants (at either 6 or 12 months of age) with IDA were rated as less positive in socioemotional behaviour, there were no differences in cognitive or motor scores. Gender and birth weight were the only

background characteristics significantly related to developmental test scores; these variables were controlled for.[11] The other study examined the effect of IDA at 6, 12 and 18 months of age on sleep at four years of age. All participants received iron treatment. Children who had IDA in infancy had altered sleep organisation throughout the night.[12] In this study age and sex were included as covariates.

Several publications were identified relating to the US cohort. Nine to ten month old infants were recruited to the study and given three months' treatment with iron. Several cross-sectional analyses were performed at recruitment. Infants with IDA had poorer motor development and mother-infant interaction during feeding.[13-15] Background factors, including infant measures and maternal demographic and health status were analysed to see if they correlated, and covariates were controlled for. One study assessed five aspects of cognitive processing at 9 months and then at 12 months. At baseline (9 months) IDA was associated with reduced object permanence (how well the child could recall which of two locations a toy has been hidden and retrieve it). A subgroup of infants who had IDA and Hb ≤105g/L also had reduced recognition memory. However, differences were no longer evident at 12 to 13 months.[16] Maternal variables that were examined for potential confounding effects included age at delivery, educational level, socioeconomic status, social support, verbal and nonverbal cognitive ability, depression, anxiety, quality of parenting and cognitive stimulation, and stressful life events. Infant variables included age at visit, gender, growth indices, feeding practices, and blood lead levels.[16] IDA also negatively affected various aspects of socioemotional behaviour at both 9 and 12 months.[17] In this study, background factors including infant and mother and family characteristics that correlated with a behavioural outcome were controlled for.[17] Infant characteristics included age, sex, birth weight, gestational age, and if they were breast fed; mother and family characteristics included maternal marital status, maternal age, maternal education, maternal depressive symptoms, maternal anxiety, maternal alcohol intake, socioeconomic status, and scores on the Home Observation for Measurement of the Environment-Revised, Life Experiences Survey and Social Support scales. Eye blinking rate was assessed in one study, although the study authors noted that the clinical importance of a lower eye-blink rate is unclear. It found that infants with IDA initially had a lower eye-blink rate than non-anaemic infants, but this increased with three months of iron therapy.[18] Background factors, including gender, birth weight, gestational age, anthropometry, and age at testing were considered as covariates. Those that were statistically significant on the regression models were retained as covariates.[18] Finally, event-related potentials (ERPs) in response to mother's face and stranger's face at 9 and/or 12 months were measured in a subgroup of the cohort. Age-appropriate ERP patterns were obtained at 9 months in iron sufficient infants. The nine month pattern was evident at 12 months in IDA group.[19] The IDA and iron sufficient groups were compared on a number of sociodemographic variables, and the potential confounding effects of age at study entry and maternal depression were taken into account.[19]

Other studies

Change et al (2010) assessed socioemotional development in three groups of non-anaemic 4-year old Chinese children: children who had IDA in infancy whose anaemia was not corrected before 24 months (chronic IDA), children who had had IDA during infancy but was corrected before 24 months (corrected IDA) and children who had never been found to be anaemic. Children who had had chronic IDA in infancy displayed less positive affect, less frustration tolerance, more passive behaviour, and more physical self-soothing in the stranger approach and delay of gratification at 4 years of age. The behaviour of children who had had corrected IDA

and those who were never anaemic was comparable.[20] The child's gender was included as a covariate in all analyses. The child's age and mother's education were also considered as potential confounding variables.

The following studies were also identified in the update search. As these studies do not add much additional information they were assessed from their abstracts only.

A prospective longitudinal study of children with IDA in India found that children with IDA have suboptimal developmental scores. The delayed development was variably reversible following oral iron therapy, depending on the severity of anaemia and age (Hb ≤7g/dL and age >24 months predicted suboptimal outcome).[21]

One longitudinal study compared neutrophil- and monocyte-apoptotic responses by flow cytometry in 49 children with IDA and 26 healthy controls aged between 6 months and 12 years. IDA patients were given oral iron supplementation. Neutrophil- and monocyte- apoptotic responses were significantly lower in IDA patients compared to the control group. However, the apoptotic response increased to the level of the control group after 15 days of iron therapy.[22]

Several studies (case series and case control) have also found a higher frequency of stroke in toddlers with IDA.[23-25]

Other cross-sectional studies are described in Table 1.

Table 1: Other relevant cross-sectional studies identified by the update search.

Study	Participants	Outcomes	Findings
Ayala et al., 2008[26]	3-15 month old infants 20 with IDA, 20 without anaemia	Psychomotor development Quantitative electroencephalography (qEEG)	*"IDA infants showed lower scores in cognition, fine motor and social/emotional areas, higher delta/theta and lower alpha power."*
Santos et al., 2008[27]	3-6 year old children 19 with IDA, 38 healthy controls	Auditory and language development	*"Anaemic children differed statistically from non-anaemic children in terms of alterations in the acoustic reflex and language development and also presented a higher prevalence of alterations in the hearing evaluation."*
Monga et al., 2010[28]	6 to 24 month old infants 25 with IDA, 25 without IDA	Visual Evoked potentials	"*A negative correlation was found between the severity of iron deficiency anaemia and latencies of waves of VEP."*
Pala et al., 2010[29]	6 to 72 month old children 49 with IDA, 100 healthy controls	Psychomotor development	DDST-II scores were abnormal in 67.3% of subjects with iron-deficiency anaemia and 15.0% of control subjects ($p < 0.01$).

UK studies

No UK studies looking at the associations between IDA and developmental outcomes published since 2006 were identified. The results of a prospective cohort study that had investigated the relationship between Hb at 8, 12 and 18 months and development at 18 months as part of Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) were published in 2001.[30] Development, assessed using the Griffiths Scales of Mental Development, was assessed in 1,141 children at 18 months, and Hb levels were available for 942 children at 8 months, 835 at 12 months and 810 at 18 months. After correcting for potential confounders, including maternal parity, gender, ethnicity, whether the child was breast fed for the first six months, whether the mother smoked during pregnancy and the highest maternal education qualification, it was found that Hb concentrations <96g/L or ≥150g/L at 8 months were associated with lower scores in the locomotor and hand/eye subscales and in the development quotient of the Griffiths Scales at 18 months.[30] Scores for the locomotor, hand/eye, and development quotient at 18 months were not associated with Hb concentrations measured at 12 or 18 months of age.[30]

***Summary*: Criterion 1 met. Although a causal association between IDA and adverse developmental outcomes has not been demonstrated, a strong association has been observed in many observational studies with potential for bias. IDA is an important health problem.**

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Prevalence

The 2006 USPSTF report stated that the average prevalence of IDA in children 1 to 2 years old in the US was 6 to 17 per 1000.[1]

Estimations of prevalence rates of IDA may be dependent on the definition used for IDA and the age range of the population assessed. The 2010 AAP clinical update referenced three recent publications with prevalence rates in Europe or the US in which the definition of IDA differed.[2] The AAP clinical report cited the US National Health and Nutrition Survey carried out in 1999-2002. Six hundred and seventy two toddlers (aged 12 to 35 months) were assessed from the general US population. The prevalence of IDA was 2.1% and the prevalence of all anaemia was 5.1%.[2] Anaemia was defined as Hb <110g/L and IDA was defined as anaemia in combination with two or more abnormal values for serum ferritin (SF) (<10µg/L), zinc protoporphyrin (ZnPP) (>1.42µmol/L red blood cells) or transferrin saturation (<10%).

The second study, Hay et al. (2004) followed a cohort of full-term Norwegian children, measuring Hb, mean cell volume (MCV) and SF at 6, 12 and 24 months.[31] At 6 months (n=278), 12 months (n=249) and 24 months (n=231) of age, 3%, 10% and 12%, respectively, had IDA, defined as Hb <110g/L in combination with SF <15µg/L. If IDA was defined as Hb <110g/L or <105g/L in combination with SF <12µg/L, the prevalence was 1% to 2% at 6 months and 2% to 5% at 12 and 24 months of age.

The third study described in the AAP clinical report, Male et al. (2001), performed a survey of 488 term infants over 11 European areas. The prevalence of IDA was 2.3% and all anaemia was 9.4%.[32]

The AAP clinical report states that data from the US National Health and Nutrition Examination Survey demonstrates that the prevalence of ID and IDA varies with ethnicity and socioeconomic status.[2]

The updated search also identified several publications looking at the prevalence of ID and IDA in children with Down's Syndrome.[33,34] The prevalence of ID and IDA in children with Down's Syndrome was reported to be similar to that of the general population.

No recent publications regarding UK prevalence of IDA were identified in the update search. A narrative article stated that the prevalence of anaemia (Hb <110g/L) in 1.5 to 2 year olds was 12% in 1995, calculated from a representative UK sample.[35] As part of ALSPAC, Hb and SF concentrations were measured in capillary blood samples from infants who were part of a representative cohort of 1,175 randomly selected children who had been born during the last six months of 1992 in the Bristol and District Health Authority. At 8 months of age, using the WHO definition of anaemia (Hb <110g/L), 23% of the surveyed children would be classified as anaemic. Using a SF cut-off of <12µg/L would classify 1.2% of the children as ID. Only 0.4% of the population fell below both cut-offs.[36] At 12 months of age, 18% of children had Hb <110g/L and 1.1% had SF <12µg/L, and 0.4% has both. At 18 months of age, 17% of children had Hb <110g/L and 4.4% had SF <12µg/L, 1.7% had both.[37]

Risk factors for IDA

The National Health and Examination Survey performed between 1999 and 2002, described in AAP clinical report found that the prevalence of IDA varied with race/ethnicity and socioeconomic status.[2]

The US CDC, in their Recommendations to Prevent and Control Iron Deficiency in the United States,[3] state that infants and children at the highest risk of IDA are:

- Premature or low birth weight babies.
- Infants fed cow's milk before 12 months of age.
- Breast-fed babies not fed iron-rich complementary foods from 6 months of age.
- Formula-fed babies fed non-iron-fortified formulas.
- Children aged 1-5 years who receive more than 25oz of cow's, goat's or soy milk per day.
- Children with special health needs, for example those with chronic infections or restricted diets.

Other risk factors for ID include prenatal/perinatal factors including anaemia during pregnancy, poorly controlled diabetes, multiple gestation, and socioeconomic factors such as low socioeconomic status and recent immigration from a developing country.[38]

Natural history

Iron status is a continuum. Iron depletion occurs when iron stores are depleted or almost depleted, but the tissues that need iron are able to maintain normal physiological functions. Iron deficiency (ID) occurs when there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain, and muscles. IDA occurs when there is an insufficient mass of red blood cells circulating in the blood due to ID. Anaemia is defined as Hb concentration two standard deviations below the mean Hb concentration for a normal population of the same gender and age. ID can exist in the absence of anaemia if the deficiency has not lasted long enough or if it has not been severe enough.[2,3,39]

As ID occurs before IDA, ID can be considered as a latent phase for IDA. However, although the risk of progression to IDA is increased with ID, ID often resolves spontaneously. For example, in one study ID (signified by a reticulocyte Hb content [CHr] <27.5pg) without anaemia was associated with increased risk of anaemia after three months or more (relative risk 9.1; 95% CI 1.04 to 78.9; p=0.01).[40] However, this was only 9% of infants with ID.

Summary: **Criterion 2 not met. The current UK prevalence of IDA is unknown. Diet, prenatal and perinatal factors and socioeconomic status all contribute to the risk of developing ID or IDA. ID, which could be considered as the latent period for IDA, often resolves spontaneously.**

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

In the 2006 review the USPSTF recommended: "*routine iron supplementation for asymptomatic children aged 6 to 12 months who are at increased risk of iron deficiency."* Under clinical considerations they state that "*premature and low birth weight infants are also at increased risk for iron deficiency."*[4]

The Evidence Synthesis for the 2006 USPSTF report concluded that

"the results of trials [of early iron supplementation in infants and children with, or at risk of, IDA] are mixed. Most trials conducted in high-risk groups within developed countries did not demonstrate any benefits for infants and preschool children, but in one trial in high-risk infants there was a transient benefit."[1]

For this report, we prioritised systematic reviews and prevention RCTs that were performed in the UK, Europe and the US. We excluded studies performed in developing countries.

Dietary intake of iron, iron fortification and iron supplementation

Recommendations

The 2010 AAP clinical report gives recommendations for the prevention of ID and IDA in term, breastfed infants; term, formula-fed infants; preterm infants; and toddlers (1-3 years of age). They recommend that term, breast fed-infants be supplemented with 1mg/kg per day oral iron from 4 months until appropriate iron-containing complementary foods are introduced into the diet. Term, formula-fed infants should be fed iron-fortified formula and have complementary iron-containing foods introduced at 4 to 6 months of age. Preterm infants should have an iron intake of 2mg/kg per day through to 12 months of age. This can be provided by iron-fortified formula or via an iron supplement starting at 1 month if breast-fed, until complementary iron-containing foods are introduced. Toddlers aged between 1 and 3 years should have an iron intake of 7mg/day. This should be met through diet, or if necessary through iron supplementation.

In addition, the US CDC also recommend:[3]

- Breast feeding to be encouraged and infants be exclusively breast-fed for 4 to 6 months after birth.
- That breast milk or iron-fortified formula is used for any milk-based part of the diet.
- That low-iron milks (including cow's milk, goat's milk and soy milk) be discouraged before 12 months of age.
- That the infant is introduced to iron-rich complementary food at 4 to 6 months, and additionally introduced to foods rich in vitamin C from 6 months of age, as vitamin C aids iron absorption.
- Children aged 1 to 5 years olds should not consume more than 24oz of cow's milk, goat's milk and soy milk.

A 2002 narrative review stated that "*in infants, the introduction of cow's milk in the first year of life is the greatest dietary risk factor for the development of iron deficiency and iron deficiency anaemia*." [38] It has been quoted that the UK recommends against the introduction of cow's milk before 1 year of age,[41] and the NHS recommend that sheep's, cow's and goat's milk be avoided during the first year.[42] NICE guidelines CG37 Postnatal care or PH11 Maternal and Child Nutrition do not make specific recommendations on the use of iron-fortified formula or the introduction of iron-rich complementary foods.[43,44] A 2008 European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) publication recommends that complementary feeding (i.e. solid foods and liquids other than breast milk or infant formula and follow-on formula) should be introduced between 17 and 26 weeks. They also state that cow's milk should not be used as a main drink before 12 months.[45]

Food fortification

The composition of infant formulae, follow-on formulae, and cereal-based foods and baby foods for infants and young children is regulated by EU law.[46,47] Infant formulae manufactured from cow's milk proteins or protein hydrolysates should contain between 0.3mg and 1.3mg iron per 100kcal. Formulae from soya protein insolates should contain between 0.45mg and 2mg iron per 100kcal. Follow-on milk should contain between 0.6mg and 2mg iron per 100kcal (0.9 to 2.5mg per 100kcal for formulae manufactured from soya protein isolates).[46] An upper limit of 3mg iron per 100kcal is described for baby foods and cereal based foods for infants and young children, although no lower limit is set.[47] Permitted iron salts for fortification are also laid out in these directives.

A number of systematic reviews analysing the effect of food fortification were identified. These are summarised below, however, the majority of the trials were performed in low income or developing countries, and often anaemia was considered as a whole rather than IDA specifically.

A 2011 Cochrane review investigated the effect of home fortification of foods with various micronutrient powders (MNP) on the health and nutrition in children under 2 years of age. It concluded that MNP reduced the risk of children going on to develop anaemia and ID, although the effect on developmental outcomes was unclear. However, all of the included trials were conducted in low income countries in Asia, Africa and the Caribbean, where anaemia is a public health problem.[48]

A systematic review investigated the impact of multiple micronutrients provided via fortification on the micronutrient status, growth, health, and cognitive development of schoolchildren. It included twelve studies which were RCTs, controlled trials (CTs) or controlled before and after studies (CBA). Eleven of the 12 studies were conducted in "*developing or transitional*" countries according to their Human Development Index 2009. Multi-micronutrient food fortification was found to consistently improve micronutrient status and reduce anaemia prevalence. However, although some studies reported positive effects on morbidity, growth, and cognitive outcomes, overall there was no change in these outcomes.[49]

Another systematic review was performed of trials of home fortification of complementary foods. When preventative trials were considered, it was found that home fortification reduced ID and the prevalence of anaemia.[50]

Iron supplementation

A number of systematic reviews (SRs) and RCTs analysing the effect of food fortification were identified. These are summarised below. Again, the majority of the trials were performed in low income or developing countries.

A 2011 Cochrane review assessed randomised or quasi randomised trials that had measured the effectiveness of intermittent iron supplementation on nutrition and development in children less than 12 years of age compared to daily supplementation or control. It included 33 trials, performed in Latin America, Africa and Asia. It found that intermittent iron supplementation was as effective as daily supplementation in improving Hb and SF concentrations, but was less effective at preventing or controlling anaemia.[51]

An SR of placebo-controlled efficacy trials involving iron supplementation in combination with two or more micronutrients (both prevention and treatment trials were included) found that the addition of multiple micronutrients only marginally improved Hb levels compared to iron

supplementation alone. However, all of the 25 included trials were performed in developing countries.[52]

Two 2009 US RCTs investigated the effect of iron supplementation from 1 to 5.5 months or from 4 to 9 months of age on the iron status of breastfed infants. Iron supplementation led to improved iron status. Neither of the above trials, due to small sample sizes, could draw conclusions on whether iron supplementation prevents ID or IDA.[53,54]

Harms of iron fortification and supplementation

The Evidence Synthesis for the 2006 USPSTF report concluded that:

"Accidental overdose is the most serious potential adverse event. Diarrhoea is a common side effect (incidence rate difference 0.05 episodes/child year, -0.03 to 0.13; p=0.21). Cohort studies have reported no important adverse effects with iron fortified formula, nor were serious side effects reported in the clinical trials of iron-fortified food or formula."[1]

A narrative review discussing the benefits and harms of iron supplementation in iron-deficient and iron-sufficient children concluded that in populations with a low prevalence of ID, general supplementation should be avoided, as excessive iron supplementation of young children has been linked with adverse effects on growth and cognitive development and with increased risk of infections. However, iron-fortified foods could still generally be recommended, but there should be limitations on the level of fortification.[55]

Many studies identified in the update search focussed on the possible negative effects of iron supplementation on growth. A detrimental effect of iron supplementation on linear growth in developed countries and with longer supplementation duration was suggested from the results of a 2006 systematic review.[56] A more recent 2009 study also found that supplementation from 4 to 6 months of age with medicinal iron was associated with a small but significant reduction in length gain and a trend towards reduced weight gain during the period of supplementation.[53] However, there were no differences in weight or length at the end of the study at 2 years of age.[53] Supplementation from 1 to 5.5 months of life was not found to affect growth.[54]. A 2008 post-hoc analysis of a RCT found no adverse effects of iron supplementation on growth at age 10 years on Chilean breast-fed infants retrospectively identified as being iron-replete. Growth effects of iron supplementation for 6 to 12 months at two different ages (6 and 12 months) and via two different iron vehicles (iron-fortified formula and iron drops) were analysed.[57]

Iron compounds for food fortification

Permitted iron salts for fortification are also laid out in EU directives.[46,47] The WHO said in 2001 that iron pyrophosphate and orthophosphate should not be used because of their poor bioavailability.[58]

Other studies identified in the update search compared the effectiveness of different forms of iron for preventing ID and IDA. In a review, Hurrell (2010) states that ferrous fumarate is currently recommended for use in the fortification of foods for infants and young children. However, they say evidence suggests that iron-deficient infants and young children may absorb iron from ferrous fumarate less well than iron from ferrous sulphate.[59] A prospective trial of two different iron compounds, iron gluconate and iron polymaltose complex, as an oral supplement, found that iron gluconate was more effective but less well tolerated .[60]

Educational interventions

A study which looked at the factors influencing iron nutrition among one-year-old healthy children in Sweden found that children whose parents received information about iron-rich foods had significantly lower levels of transferrin receptor, indicating better iron status, than the children whose parents did not receive information about iron-rich foods (p=0.01).[41]

A Canadian RCT investigated whether a brief, paediatric office based bottle-weaning educational intervention for parents of 9 month-old children could reduce bottle use and iron depletion at 2 years of age. The rationale for this intervention was that previous observational studies have demonstrated an association between bottle-feeding beyond 15 to 18 months of age and ID. Both groups received counselling on healthy nutrition, and in addition parents in the intervention group received a "*sippy*" cup to use rather than a bottle and a protocol to introduce it. The parents were also told to limit the amount of milk their child received to 16oz per day. It found that although the prolonged bottle use was reduced in the group receiving the intervention, there was no difference in iron depletion between the two groups.[61]

Umbilical cord clamping

Several studies were identified that assessed the effect of timing of umbilical cord clamping on iron status of infants. Two recent systematic reviews have found beneficial effects on haematological and iron status and risk of anaemia associated with delaying cord clamping (variably defined as either after one or two minutes).[62,63] A recent RCT in Sweden found that delayed cord clamping (≥3 minutes after delivery) resulted in improved iron status and reduced prevalence of ID at 4 months of age and reduced prevalence of neonatal anaemia at 2 days of age.[64] In April 2011 the Royal College of Obstetricians and Gynaecologists (RCOG) added an addendum to the Greentop Guideline 'Postpartum Haemorrhage, prevention and management'.[65] The RCOG guideline now states that:

"The cord should not be clamped earlier than is necessary, based on clinical assessment of the situation."

Summary: **Criterion 3 partly met. There are recommendations for iron intake, the introduction of complementary foods, the levels of iron fortification and the timing of umbilical cord clamping in the UK and other countries. Iron status of infants may be improved by increased information about iron-rich foods. We did not identify studies reporting the extent to which recommendations were followed or interventions implemented in the UK.**

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable.

5. There should be a simple, safe, precise and validated screening test

In the summary of screening recommendations, the 2006 USPSTF report states that *"there is good evidence that Hb is a sensitive test for iron deficiency anaemia, but it has low specificity because the majority of anaemias in childhood are not caused by iron deficiency."*[4]

The 2010 AAP clinical report stated that "*no single measurement is currently available that will characterise the iron status of a child*."[2] The reports says that as the prevalence of ID and IDA

have reduced in industrialised nations, a diagnosis of IDA cannot be made on the basis of Hb concentration alone, as other causes of anaemia account for proportionally more cases.[2]

Existing US guidelines that advocate screening for IDA in infants and children recommend that Hb or Hct be measured , although the WHO also state that in resource-adequate or developed countries additional tests such as SF or transferrin saturation levels could be measured to detect mild forms of ID or iron overload.[2,3,58]

A drop in Hb or Hct levels only occurs once anaemia is present. To determine the cause of anaemia and to detect ID, the latent phase for IDA, iron status needs to be determined. The US CDC state that:

"additional measurement of indicators of iron deficiency (e.g., erythrocyte protoporphyrin concentration and serum ferritin concentration) to increase the positive predictive value of screening are now suitable approaches to assessing iron deficiency among most U.S. children."[3]

Tests for iron deficiency

There are a wide range of haematological and biochemical indicators of iron status which can be measured. These summarised in Table 2. Of the presently available tests the AAP clinical update recommend that to establish a diagnosis of ID, SF combined with C-reactive protein (CRP), or reticulocyte Hb (CHr) levels could be measured. To diagnose IDA, these tests should be combined with Hb concentration, or the response to iron-replacement therapy should be monitored.[2] The AAP also supports the development of the serum or plasma transferrin receptor 1 (TfR1) assay.[2] A narrative review from 2008 recommended that where feasible, Hb, SF and, if CRP is elevated, TfR and/or zinc protoporphyrin (ZnPP) should be measured.[66]

A number of these factors have been discussed as possible screening tests for ID. However, many of the biochemical tests are "*impractical for screening in the ambulatory setting*."[40] This is either due to biological variability, their non-availability in the ambulatory setting or due to lack of standardisation.[39,40,66]
Serum iron and transferrin saturation vary diurnally, with dietary intake, and in chronic disease.[39,66] SF levels are directly proportional to iron stores in healthy individuals; measurement is widely available and well standardised; and it has been found that it can distinguish people with ID from iron sufficient people in a population assessment.[39,66,67] However, SF is an acute phase protein, and is increased, independent of iron status, by acute or chronic inflammation. Its diagnostic value in children has also been questioned.[68] Serum transferrin receptor (TfR) levels are not significantly affected by the acute phase response, however, the commercial assays are high cost and measurement of TfR concentrations using different methods has not been fully standardised.[66,69]

Zinc protoporphyrin (ZnPP) has been investigated as a screening test. Erythrocyte protoporphyrin is the immediate precursor of Hb. Zinc replaces the missing iron during formation of the protoporphyrin ring in ID erythropoiesis, causing levels of ZnPP to increase. The ratio of ZnPP/haem can be measured by haematofluorometry using a drop of whole blood. It is reportedly a sensitive test for detecting ID, but with limited specificity.[66] A cross-sectional study in the US found that ZnPP was more sensitive (sensitivity, 28%) but less specific (specificity, 72%) than Hb (sensitivity 11%, specificity 94%) for identifying ID in preschool-aged children.[70] The related measure, erythrocyte protoporphyrin, was found by receiver operating characteristic analysis of data from the third National Health and Nutrition Survey to be a better screening tool for ID than Hb in children aged 1 to 5.[71]

CHr, a haematological marker, has also been suggested as a screening test. Reticulocytes are the earliest erythrocytes released into the peripheral blood, and exist for between 24 and 48 hours before maturing. Levels of Hb in reticulocytes respond rapidly to decreased levels of iron. In a retrospective laboratory analysis of 210 children with a mean age of 2.9 years, in which various potential markers of ID were measured, CHr was the strongest predictor of ID and IDA in children. A cut-off of 26pg CHr had a sensitivity of 70% and specificity of 78% for ID and a sensitivity of 83% and specificity of 75% for IDA.[68] A cut-off for CHr of <28.55pg had a sensitivity of 76.6% and a specificity of 78.4% for diagnosing ID in 6 to 24 month old children in Lithuania.[72] In a study of 9 to 12 month old children presenting to a urban, hospital based, primary care clinic in the US for well-child or non-urgent visits found that a threshold of 27.5pg for CHr had a sensitivity of 83% and a specificity of 72% for predicting ID (positive predictive value [PPV] 28%, negative predictive value [NPV] 97%) compared with Hb <11g/dL which had a sensitivity of 26%, specificity of 95% (PPV of 43% and a NPV of 91%).[40] In this study, patients were re-screened at least three months later. A CHr <27.5pg without anaemia was associated with the development of anaemia (relative risk 9.1; 95% CI 1.04 to 78.9; p=0.01).[40] However, although CHr is a sensitive marker for ID and is independent of inflammation, its specificity is limited by other haematological conditions. It also has the disadvantage that few analysers are presently available that can measure it, although good levels of agreement are seen across available analysers.[73] Larger multicentre studies are necessary to determine whether measurement of CHr is effective for screening for ID or IDA.

Table 2: The main biochemical indicators of iron deficiency. Adapted from Zimmermann, 2008[66] and WHO, 2007[39].

	Description	Commonly used methods of measurement	Comments
Bone marrow iron (hemosiderin)	Indicates body iron stores.	Microscopical examination of stained cells.	Gold standard for diagnosing ID. Invasive and traumatic to collect.
Haemoglobin (Hb)		Cyanmeta using colorimeter or spectrophotometer or azidemethhaemoglobin using e.g. HemoCue®.	Simple to measure. Used alone, has low specificity and sensitivity. Anaemia occurs without ID, and changes in Hb concentration with ID occur late. Thresholds vary by age, gender, pregnancy, altitude, and with ethnicity.
Haematocrit (Hct)	Hct indicates the proportion of whole blood occupied by red blood cells.	Centrifugation in capillary tube or automated flow cytometry.	Same as Hb.
Mean corpuscular volume (MCV)	Small microcytic red cells are reflective of insufficient iron delivery to bone marrow.[74]	Calculated from the Hct and red blood cell count or automated flow cytometry.	A reliable, but relatively late indicator of ID. Low values can also be due to thalassemia and/or inflammation.
Mean cell haemoglobin (MCH)	Haemoglobin in an average red blood cell. If low, hypochromic.	Calculated from the Hb concentration and red blood cell count or automated flow cytometry.	Slow to respond to ID.
Red blood cell distribution width (RDW)	Red blood cell distribution width is calculated by dividing the standard deviation of red blood cell volume by MCV and multiplying by 100. High in ID.	Automated flow cytometry.	
Blood reticulocyte Hb concentration (CHr)	Concentration of Hb in new (18-26 hours old) red blood cells (reticulocytes).	Automated flow cytometry.	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis. False normal values can occur when MCV is increased and in thalassemia. Few analysers can measure this.[75]
Serum or plasma iron	Iron bound to transferrin in the blood.	Colorimetry (sample from non-EDTA tube).	Varies diurnally and after meals. Low values in chronic disease.
Whole blood zinc protoporphyrin (ZnPP)	Erythrocyte protoporphyrin is the immediate precursor of Hb. Zinc replaces the missing Fe during formation of the protoporphyrin ring in IDE, causing ZnPP to increase.	Fluorescence spectrophotometry or portable Aviv® haematofluorimeter.	Lead poisoning can elevate values, particularly in urban/industrial settings. ZnPP can also be increased by anaemia of chronic disease, chronic infections and inflammation, haemolytic anaemias or haemoglobinopathies. Red cells should be washed before measurement because circulating factors, including serum bilirubin, can spuriously

			increase values.
Erythrocyte protoporphyrin (EP)	Related measure to ZnPP.	Usually estimated from ZnPP.	As ZnPP.
Serum or plasma ferritin (SF)	In healthy individuals, SF is directly proportional to iron stores: 1mg/L SF corresponds to 8–10mg body iron or 120mg storage iron/kg body weight.	Immunoassay or immunoturbidometry.	Widely available and well standardized. As an acute phase protein, SF is increased independent of iron status by acute or chronic inflammation; also unreliable in subjects with malignancy, hyperthyroidism, liver disease, or heavy alcohol intake.
Serum or plasma total iron binding capacity (TIBC)	Total capacity of circulating transferrin bound to iron.	Colorimetric assay of amount of iron that can be bound to unsaturated transferrin in vitro; determination from transferrin concentration measured immunologically.	Large overlap between normal values and values in ID.
Serum or plasma transferrin saturation	Proportion of transferrin bound to iron.	Ratio of plasma/serum iron to total iron-binding capacity.	Influenced by factors that affect serum iron.
Serum or plasma transferrin receptor (TfR)	TfR is a transmembrane glycoprotein that transfers circulating Fe into developing red cells. <80% of TfR in the body is found on erythroid precursors. A circulating, soluble form of TfR consists of the extracellular domain of the receptor. The total mass of cellular TfR and, therefore, of serum TfR depends both on the number of erythroid precursors in the bone marrow and on the number of TfRs per cell, a function of the iron status of the cell.	Immunoassay or immunoturbidometry.	Also increased by conditions with enhanced erythropoiesis. Not significantly affected by the acute phase response, but may be influenced by thalassemia, other causes of anaemia, malaria, age and ethnicity. High cost. Age-related data for TfR in children is scarce, and levels measured are dependent on the method used (assay specific).
Body iron stores (ratio of TfR/SF)	This ratio can be used to quantitatively estimate total body iron. The logarithm of this ratio is directly proportional to the amount of stored iron in iron-replete subjects and the tissue iron deficit in ID.	Ratio of transferrin receptor to ferritin.	Cannot be used in individuals with inflammation because the SF may be elevated independent of iron stores. Is assay specific (as with TfR). Although only validated for adults, is often used in children.
Hepcidin	Regulator of iron absorption from the gut.	Immunoassay.	Assay methods and interpretation of results under development.

Summary: **Criterion 5 not met. Hb or Hct levels are currently recommended by WHO and a number of US bodies to screen for IDA. However, although Hb and Hct are very sensitive for detecting anaemia, they cannot distinguish anaemia caused by ID from other causes of anaemia, and therefore have a low positive predictive value in populations with a low prevalence of IDA. They also only diagnose IDA once anaemia is present, and therefore cannot be used to screen for the prevention of IDA. Screening with a number of other markers of iron status has been discussed. Measurement of SF, ZnPP and CHr could be potentially used to screen for IDA. Diagnostic tests exist, but a simple, non-invasive test suitable as a screening test for IDA in young children was not identified.**

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

No publications regarding the distribution of test values in the UK population or cut-off values for defining IDA in the UK published since 2006 were identified in the update search.

Distribution of Hb and Hct values in the target population.

No publications since 2006 were identified in the update search detailing the distribution of Hb or Hct values in children in the UK. Older data exist, for example, Hb and SF concentrations in capillary blood samples were measured as part ALSPAC in a random sample of children born during the last six months of 1992 in the Bristol and District Health Authority. At 8 months of age, Hb values were normally distributed with a mean (SD) 117 (11)g/L (95% confidence interval 116 to 118g/L) and range from 72 to 153g/L.[36] Hb concentrations were positively related to the child's weight at 8 months.[36] At 12 months of age, mean Hb concentration (SD) was 118 (10)g/L, and at 18 months of age 117 (10)g/L.[37] None of the variables investigated were associated with Hb concentration at 12 months of age. At 18 months of age, the gender of the child and the mother's highest educational qualification were significantly associated with Hb concentrations. Girls had higher Hb concentrations than boys, and Hb concentration followed a U shaped curve with maternal education.

Cut-off level for defining anaemia

Anaemia occurs when Hb concentration falls two standard deviations below the mean Hb for a normal population of the same gender and age range.[58] The WHO define Hb and Hct levels below which anaemia is present in a population as 110g/L for Hb and 0.33% for Hct, for children aged 6 months to 59 months.[58]The AAP clinical report states that on the basis of the 1999-2002 US National Health and Nutrition Examination Survey, anaemia is defined at a Hb concentration of less than 110g/L for children aged 12 months to 35 months.[2]

Publications from 1996 and 1999 from ALSPAC suggested different cut-offs for British infants. At 8 months of age, a more representative cut-off for anaemia was suggested to be an Hb concentration <97g/L.[36] At 12 and 18 months the suggested cut-off was Hb <100g/L.[37] See Table 3.

Table 3: Children fulfilling the ALSPAC cut-off criteria for IDA in the ALSPAC study

	Hb only Hb <100g/L		Hb and Ferritin Hb <100g/L; SF <16 (at 12 months) and 12µg/L at 18 months		Positive predictive value of Hb cut-off	
Age of infant (months)	12	18	12	18	12	18
% of children fulfilling ALSPAC criteria	5%	5%	0.5%	0.6%	10%	12%

Distribution of values for iron markers in the target population

No publications were identified in the update search detailing the distribution of other iron status marker values in children in the UK published since 2006. The ALSPAC study found that SF concentrations were log normally distributed in a randomly selected sample of children born during the last six months of 1992 in the Bristol and District Health Authority area. At 8 months of age the geometric mean was 38.5µg/L (95% CI 37.0 to 39.9, range 7.1 to 224µg/L).[36] SF concentrations were positively associated with birth weight and female gender, and negatively associated with the child's weight at 8 months.[36] At 12 months of age the geometric mean was 32.8µg/L and at 18 months of age 27.5µg/L.[37] At 12 months of age, SF concentrations were positively associated with female gender of the study child and birth weight, and negatively associated with weight on attendance at the clinic. At 18 months of age, SF concentrations were still associated with birth weight and weight on attendance at the clinic but no longer with gender.

Cut-off levels for defining ID/anaemia due to ID

The thresholds for several biomarkers for identifying ID, given in a 2008 native review,[66] are shown in Table 4. However, these definitions do not seem to have been universally accepted as many studies have used alternative criteria to diagnose ID or IDA.

Publications from the ALSPAC study suggested cut-off levels for iron deficiency in British infants of SF <16µg/L at 8 months of age, <16µg/L at 12 months of age and <12µg/L at 18 months of age.[36,37]

Table 4: Cut-off values for the main biochemical indicators of iron deficiency. Adapted from Zimmermann 2008.[66] * Using RAMCO® ELISA for transferrin receptor.

	Threshold indicating ID
Haemoglobin (Hb)	6 months to 59 months: 110g/L
Haematocrit (Hct)	6 months to 59 months: 0.33%
Blood mean corpuscular volume (MCV)	No threshold given for young children
Blood reticulocyte Hb concentration (CHr)	In infants and young children <27.5pg
Serum or plasma iron	<40–50µg/dL
Whole blood zinc protoporphyrin (ZnPP)	On unwashed erythrocytes in children <5y: >61µmol/mol of haem No threshold given for this age range for washed erythrocytes
Serum or plasma ferritin (SF)	<5 years: <12µg/L
Serum or plasma total iron binding capacity	>400µg/dL
Serum or plasma transferrin saturation	<15%
Serum or plasma transferrin receptor	Varies with assay
Body iron stores	Negative values indicate tissue iron deficit*

A review is currently being conducted by the WHO of a number of iron status indicators.[76]

Summary: **Criterion 6 not met. A simple, non-invasive test suitable as a screening test for IDA in young children in the UK has not been identified. Hb and Hct are currently recommended by WHO and a number of US bodies to screen for IDA. The Hb value of 110g/L has been adopted to define anaemia in the 12 to 35 month age group in the US. However, different Hb cut-off values were suggested for IDA in the UK by the ALSPAC study from the 1990s. Cut-off values for other markers of iron deficiency have been suggested. No recent publications regarding the distribution of test values in the UK population were identified in the update search, nor UK guidance on appropriate cut-offs for defining IDA.**

7. The test should be acceptable to the population

Acceptability of Hb test

Blood samples to determine Hb concentrations can be determined by finger-prick or heel prick (for newborns). No studies were identified in the update search assessing the acceptability of the test. A newborn heel prick test is already performed in the UK for collecting blood spots used for neonatal screening.

Acceptability of tests of iron status

Measurement of the suggested biomarkers for assessing iron status will require blood samples. The minimum volume required for one analysis of several biomarkers is shown in Table 5.

Table 5: Minimum volume for one analysis of selected biochemical indicators. Extracted from WHO 2007[39]

Indicator	**Minimum volume required for one analysis**
Haemoglobin	50µl whole blood
Zinc protoporphyrin	50µl whole blood
Mean corpuscular volume	300µl whole blood
Transferrin receptor	100µl serum or plasma
Ferritin	100µl serum or plasma
C-reactive protein	20-50µl serum or plasma

No studies identified in the update assessing the acceptability of these tests. However, one narrative review stated that "*most family physicians or paediatricians are hesitant to perform extensive iron studies on young children, particularly infants, due to the need for venepuncture to obtain an adequate sample*."[75]

Summary: **Criterion 7 not met. The ideal test to screen for IDA and therefore to assess for acceptability has not yet been identified. A heel prick test is likely to be acceptable to the population, as it is already in use. However, no studies were identified in the update search assessing the acceptability of any test for IDA.**

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

No UK publications or guidelines were found.

The 2010 AAP clinical report recommend that if Hb concentration is less than 11.0g/dL at 12 months of age or if children are at high risk of dietary ID then measurement of SF and CRP levels, or CHr concentration should be performed. Alternatively, if a child has mild anaemia (Hb 10 to 11g/dL) then response to iron-replacement therapy can be used to confirm IDA.[2]

The US CDC recommends that a positive anaemia screening result should be repeated for confirmation. The response to one month's treatment with iron drops (3mg/kg per day) should be monitored. An increase in Hb concentration of ≥1g/dL or in Hct ≥3% confirms the diagnosis of IDA, and treatment should be continued for a further two months. If no response is seen MCV, red blood cell distribution width (RDW) and SF levels should be measured to determine the cause of anaemia.[3]

The WHO recommend that Hb or Hct response to iron administration or SF, EP, or TfR levels be used to confirm or diagnose IDA.[58]

A narrative review from 2008 recommended that where feasible, Hb, SF and, if CRP is elevated, TfR and/or ZnPP should be measured.[66]

Summary: **Criterion 8 not met. No UK publications detailing the policy on further diagnostic investigation of individuals with a positive test result were found. US and international guidelines which advocate screening recommend that a positive Hb or Hct result be followed up with further tests of iron status, or by a trial of therapeutic iron.**

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Not applicable.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

In the 2006 summary of screening recommendations the USPSTF states that *"the USPSTF found no evidence that universal or selective screening for iron deficiency anaemia in asymptomatic children results in improved health outcomes. The USPSTF found poor evidence (conflicting*

studies) of the effectiveness of interventions that demonstrate improved health outcomes, such as developmental status, in asymptomatic children."[4]

The 2006 USPSTF report concluded that:

"Iron supplementation in infants aged 3 to 6 months improves growth and weight gain in anaemic, malnourished children aged 7 to 10 years in developing countries. There is no evidence directly related to screening in the U.S."[1]

In the clinical considerations section, they state that *"iron deficiency anaemia is usually treated with oral preparations. The likelihood that iron deficiency anaemia identified by screening will respond to treatment is unclear because many families do not adhere to treatment and because the rate of spontaneous resolution is high."*[4]

For this report, we prioritised systematic reviews and prevention trials that were performed in the UK, Europe and the US. We excluded studies performed in developing countries.

Supplementary intake of iron

In the US, ID is usually treated with 3mg/kg elemental iron given orally.[3,38] Absorption is suggested to be improved if it is taken with a source of vitamin C, such as orange juice.[38] It is recommended that response to therapy should be assessed after a month, and if ID/IDA confirmed then treatment continued for a further two months.[3,38] The results of a recent case-series in the US suggested that parenteral iron (iron sucrose) is a safe and effective means to treat ID in children under 18 years of age who cannot receive or do not respond to oral iron.[77]

Effect on ID/IDA

A narrative review suggests that a therapeutic trial of oral iron is the gold standard for diagnosing ID, with a positive response confirming diagnosis.[38] This suggests that therapeutic iron is considered to have a beneficial effect on iron status.

A protocol for a Cochrane review investigating the effect of iron supplementation on IDA in children has been published.[78] It will look at RCTs comparing any form of iron supplementation compared to placebo, or other current regimens used to treat IDA, and comparisons of different forms of iron supplementation. Primary outcomes will be mortality, morbidity, and adverse events and secondary outcomes will be symptom improvement, improvement of blood test indices (such as Hb), improvement of iron store indices, influence on growth and development, health related quality of life and economic outcomes.

A systematic review of randomised placebo controlled trials assessing the effect of combining iron supplementation with two or more micronutrients on Hb concentration in children identified 25 trials published before February 2006. Both prevention and treatment trials were included. However, all of the 25 included trials were performed in developing countries. The systematic review concluded that the addition of multiple micronutrients to iron supplementation only marginally improves Hb response.[52]

A systematic review of home fortification of complementary foods found that micronutrient powders such as Sprinkles® were as effective as iron drops and were better accepted with fewer side effects.[50]

Effect on complications of IDA

A 2007 narrative review by McCann and Ames[6] cited by the 2010 AAP clinical update[2] described that cognitive and behavioural outcomes of children with IDA improved with iron treatment in

children >2 years of age. However, resistance to treatment was observed in children <2 years of age.

A 2001 Cochrane systematic review (edited in 2009) concluded on the basis of five trials that there was no evidence that treatment of young children with IDA had an effect on psychomotor development within 5 to 11 days, and of the two longer term trials, one trial reported developmental benefits after iron therapy, while the other reported no benefit.[5] IDA has previously been associated with impaired growth. A 2006 systematic review of RCTs found no statistically significant effect on any anthropometric variable with iron supplementation.[56]

A number of the cohort studies which have shown an association between IDA and a variety of adverse effects have also looked at the effect of treatment. Treatment has been found to either have a positive effect or no effect compared to pre-treatment measures. In some cases the post-treatment outcomes have been compared to healthy controls. However, these studies did not have a no intervention control group.

Studies showing no effect of treatment

The Costa Rican cohort study found that chronic ID in infancy (diagnosed at 12 to 23 months) was associated with reduced motor scores at 11-14 years of age, and impaired cognition at 19 years of age, despite correction of ID.[8-10] In the Chilean cohort, alterations in sleep organisation were observed at 4 years of age in children who had IDA in infancy, despite all children receiving therapeutic iron.[12] In the US cohort, IDA negatively affected various aspects of socioemotional behaviour at both 9 months of age and after iron therapy at 12 months of age,[17] and a 9 months of age appropriate event related potential (ERP) pattern was evident at 12 months of age in the IDA group.[19]

Studies showing positive effect of treatment

In the US cohort, cognitive processing was impaired in 9 month old children with IDA, but no differences were seen between non-anaemic and previously anaemic children at 12 months after iron therapy.[16] Eye blinking rates were initially lower in infants with IDA than non-anaemic infants, but increased following therapy.[18] The socioemotional development of children who had had corrected IDA and those who were never anaemic was comparable in a Chinese study. This study also included a group of 27 infants whose IDA was not corrected before 24 months, this group showed behavioural differences.[20] Delayed development was not consistently reversible following oral iron therapy in an Indian study. The outcome was dependent on the severity of anaemia and age (Hb ≤7g/dL and age >24 months predicted suboptimal outcome).[21] Neutrophil- and monocyte-apoptotic responses also responded to 15 days of iron therapy and were similar to those of a healthy control group.[22]

Other interventions

An RCT by Lozoff et al. (2010) investigated whether a home based intervention, designed to foster child development by supporting the mother-infant relationship, could improve cognitive and emotional scores in infants with IDA who were treated with oral iron therapy.[11] Chilean infants with IDA and control infants (enrolled at 6 and 12 months old) received oral iron and were randomly assigned to surveillance or home based intervention for one year. Infants with IDA (at both 6 and 12 months) were rated as less positive in socioemotional behaviour at baseline, although cognitive and motor scores were similar. Infants with IDA who received the intervention had developmental trajectories over the duration of the trial comparable to those of non-anaemic infants in the intervention and control groups, and higher than infants with IDA randomised to the control group. However, even with the intervention, no catch up was

observed in socioemotional behaviour. Therefore, the authors concluded that a home-based intervention improved cognitive and socioemotional scores in infants with IDA, but socioemotional differences remained between infants with and without IDA.

Early treatment versus late treatment

Several narrative reviews have stated that the adverse effects of ID can be prevented and or reversed with iron supplementation early in development or before ID becomes severe or chronic.[79,80]

The US cohort described above were screened and treated for IDA at 9 months, and improvements were seen on some outcomes.[17-19] In contrast, ID was diagnosed and treated at 12-23 months in the Costa Rican study, and long-term adverse effects were seen.[7-10] This could be because children were iron deficient for some time. Socioemotional development of 4-year old Chinese children who had IDA in infancy whose anaemia was not corrected before 24 months was impaired, whereas the behaviour of children who had had corrected IDA was comparable to those who were never anaemic.[20] An Indian study found that delayed development was reversible dependant on the severity of anaemia and the age of the child (Hb ≤7g/dL and age >24 months predicted suboptimal outcome).[21]

***Summary*: Criterion 10 not met. Iron status can be improved with therapeutic iron. The reported effect of treatment on complications of IDA including cognition is conflicting. There is some evidence from observational studies without a no intervention control group that the outcomes for patients identified through early detection, or those receiving early treatment compared with late treatment, are better.**

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

No publications relevant to this question were identified in the update search.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

The 2010 AAP clinical report stated that:

"if IDA (or any anaemia) or ID has been confirmed by history and laboratory evidence, a means of carefully tracking and following infants and toddlers with a diagnosis of ID/IDA should be implemented. Electronic health records could be used not only to generate reminder messages to screen for IDA and ID at 12 months of age but also to document that IDA and ID have been adequately treated once diagnosed."[2]

However, one retrospective cohort study of 4984 children in the US found poor follow-up testing and poor documentation of improved Hb concentration.[81] For those who screened positive for ID (as defined by one of 9 different criteria), around 25% had a repeat blood count within 6 months, and between 4.4% to 11.6% had documented correction of their ID. A UK study performed a retrospective audit of paediatric patients, aged between one month and 16 years, in an English district general hospital.[82] Recognition, treatment and follow-up of an abnormal red cell index which may indicate ID, specifically decrease in mean corpuscular volume (MCV) with no definite explanation, was analysed. The study found that abnormal indices were frequently missed, or no follow-up or treatment occurred. Across two audits an average of 21%

of patients with test results documented as abnormal received treatment and/or follow-up. This publication also quoted another study (Pusic et al., 2005[83]) that also looked at detection and follow-up rates of microcytosis in all children aged to 36 months presenting to a Paediatric Emergency Department in Canada. Treatment or follow-up was only documented for 35% of the children with MCV.

Summary: **Criterion 12 not met. From one UK publication identified in the update search detailing an audit of one English district hospital, it appears that recognition, management and treatment of ID is not yet optimised.**

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

The 2006 USPSTF report concluded that:

"in controlled trials and time-series studies, screening and treatment for IDA can reduce the prevalence of IDA in high risk populations, but there are no data that directly link screening with better neurodevelopmental outcomes."[1]

In the clinical considerations section, they state that *"the likelihood that iron deficiency anaemia identified by screening will respond to treatment is unclear because many families do not adhere to treatment and because the rate of spontaneous resolution is high."*[4]

No RCTs of screening were identified in the update search.

Summary: **Criterion 13 not met. There is no evidence from RCTs that screening for IDA is effective in reducing mortality or morbidity.**

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

No publications relevant to this question were identified in the update search.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

The 2006 USPSTF report concluded that there was no evidence about the adverse effects of screening infants and children for IDA. Cost, time, anxiety and the risk of identifying false positives were listed as potential harms of screening. The small potential harms of treatment with oral iron include gastrointestinal symptoms and unintentional overdose.[1]

No publications weighing up the benefits and harms of IDA screening were identified in the update search.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

Only one relevant US study modelling the cost benefit of different screening tests for ID was identified in the update search. It compared the cost-benefit profile of screening and treatment of ID in 9- and 12-month old infants using CHr, with Hb alone.[84] In the model, the prevalence of ID was assumed to be 9%. Sensitivity and specificity values for CHr and Hb tests for ID determined in a previous study were used (CHr <27.5pg sensitivity 83%, specificity 72%; Hb <11g/dl sensitivity 26%, specificity 95%).[40] Costs of the tests were estimated from the laboratory fee schedule form the Centres for Medicare and Medicaid Services (CHr, $11; Hb, $5). Three month courses of iron therapy were prescribed for subjects with ID and with anaemia, at an estimated cost of $61. In their base case, they found that the incremental cost of screening using CHr was $22 per patient, and $400 dollars per case of anaemia prevented, NNT=20. In a 10-year time horizon incorporating the risks of neurocognitive delays, the cost of screening using CHr was $280 per case of anaemia prevented. It should be noted that this model had a number of assumptions, including that all CHr true-positive results would progress to anaemia. When a rate of 40% spontaneous resolution was included, CHr screening cost $740 per case of anaemia prevented. It is also difficult to estimate the risk or cost of any long-term neurocognitive effect (in the longer-term model). In this model, they assumed a 10% annual risk of neurocognitive delay significant enough to require some degree of additional health care use in infants with untreated ID, and estimated an annual disability cost of $500 for children with neurocognitive delays. No disability was assumed for any patients who received follow-up testing. They estimated the rate of follow-up testing as 60%.

Summary: **Criterion 16 not met. Only one US study was identified modelling the cost of screening tests ID. It is unclear what the cost of screening for IDA in the UK would be.**

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

No publications relevant to this question were identified in the update search.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

No publications relevant to this question were identified in the update search.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

No publications relevant to this question were identified in the update search.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

No documents giving evidence-based information explaining the consequences of testing, investigation and treatment, nor plans to implement them, were identified in the update search.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

No publications relevant to this question were identified in the update search.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

Not applicable.

Conclusions

The condition

Iron status is a continuum. Iron depletion occurs when iron stores are depleted or almost depleted, but the tissues that need iron are able to maintain normal physiological functions. Iron deficiency (ID) occurs when there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain, and muscles. Iron deficiency anaemia (IDA) occurs when ID is severe enough to affect red blood cell production, and to cause haemoglobin concentration in the blood to fall two standard deviations below the mean for a normal population of the same gender and age. Diet, prenatal and perinatal factors and socioeconomic status all contribute to the risk of developing IDA. ID, which can be considered as the latent period for IDA, often resolves spontaneously. Children aged between 9 and 18 months are at the highest risk of IDA due to a rapid rate of growth combined with low dietary intake of iron. A slower rate of growth combined with the introduction of a more diversified diet reduces the risk of IDA after 24 months of age. Other dietary changes not needing to be prescribed by a health professional will resolve ID.

IDA during infancy has been associated with several negative outcomes in many observational studies. However, a causal association between IDA and adverse developmental outcomes has not been demonstrated. This is attributable to potential confounding due to socioeconomic status and due to the presence of anaemia. Despite this, IDA can be considered to be an important health problem.

Prevention

Recommendations exist on iron intake, the introduction of complementary foods, the levels of iron fortification and the timing of umbilical cord clamping. However, the extent to which recommendations are followed or interventions implemented in the UK is unknown. The iron status of children under five years may be further improved with increased information about iron-rich foods.

The test

Haemoglobin (Hb) or haematocrit (Hct) levels are currently recommended by WHO and a number of US bodies to screen for IDA. The Hb value of 110g/L has been adopted to define anaemia in the 12 to 35 month age group in the US. However, although Hb and Hct are sensitive tests for detected anaemia, they cannot distinguish anaemia caused by ID from anaemia due to other causes, and therefore have a low positive predictive value in populations with a low prevalence of IDA. They also only diagnose IDA once anaemia is present, and therefore cannot be used to screen for the prevention of IDA. Screening with a number of other markers of iron status has been discussed. Measurement of serum ferritin, zinc protoporphyrin or blood reticulocyte Hb concentration could be potentially used to screen for IDA, and cut-off values for these markers have been suggested.

Therefore, although diagnostic tests for ID and IDA exist, a simple, non-invasive test suitable as a screening test for young children was not identified.

Treatment

Oral iron is effective at treating ID and IDA. The reported effect of treatment on complications associated with IDA is conflicting. There is some evidence from observational studies without a

no intervention control group that the outcomes for patients identified through early detection, or for those receiving early treatment compared with late treatment, are better.

Screening

There is no evidence from randomised trials that screening for IDA is effective in reducing mortality or morbidity. In addition, it appears that recognition, management and treatment of ID is not yet optimised in the UK. The potential cost of screening in the UK is unknown.

Implications for policy

The updated evidence published since 2006 does not support a change in national policy regarding screening for iron deficiency anaemia in children less than 5 years of age.

Implications for research

The evidence update highlights areas where further research is required:

- **The condition.** Further studies are required to support a causal link between IDA and the adverse effects it is associated with, for example poor neurocognitive outcomes. The prevalence of IDA in the UK needs to be established.
- **Prevention.** The measures that are recommended to prevent IDA in this age group and their uptake need to be evaluated. Qualitative research into the acceptability, barriers and facilitators to iron supplementation in infancy and childhood could be performed.
- **The test.** Further development of tests suitable for screening is required. The diagnostic accuracy of the test needs to be determined in populations similar to the UK population. The acceptability of the test to the population should be ascertained.
- **Treatment.** Although there is some conflicting evidence for improvement of adverse outcomes associated with IDA with treatment, further studies are required to establish whether treatment of IDA identified by screening does improves outcomes, and whether early treatment is better than late treatment.
- **Screening.** RCTs demonstrating that screening leads to improves outcomes need to be performed. The best age to screen for IDA also needs to be determined.

Methodology

Search strategy

BACKGROUND: A literature search was performed to find citations on screening for iron deficiency anaemia published since the National Screening Committee's consideration of the topic in 2001 the search was therefore performed from 2000 onwards.

SOURCES SEARCHED: Medline, Embase, the Cochrane Library, PsycINFO, Cinahl, Web of Science and Centre for Reviews and Dissemination (CRD) databases. A simple search of the metaRegister of Clinical Trials, ClinicalTrials.gov and the HTA database for work that is currently going on but not yet published, was also performed.

DATES OF SEARCH: January 2000 to 4 January 2010

SEARCH STRATEGY: Medline Ovid

The strategy was designed to be as broad as possible to ensure nothing related to screening for iron deficiency anaemia was missed. As a result many hits that were not relevant were also retrieved.

1. Infant/
2. Infant, newborn/
3. exp Child/
4. neonat$2.tw.
5. newborn.tw.
6. child$3.tw.
7. infan$2.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Anemia, Iron Deficiency/
10. (anemi$ or anaemi$).tw.
11. iron deficien$.tw.
12. 9 or 10 or 11
13. Mass Screening/
14. Neonatal Screening/
15. screen$3.tw.
16. detect$3.tw.
17. (test or tests or testing).tw.
18. exp "Sensitivity and Specificity"/
19. (sensitivity or specificity).tw.
20. exp Patient Acceptance of Health Care/
21. exp Nutrition Therapy/
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp Child Development/
24. exp Neurobehavioral Manifestations/
25. Developmental Disabilities/
26. Educational Status/
27. (development$2 and (assessment or motor or psychomotor or delay$ or outcome$ or impair$ or general or mental or quotient$)).tw.
28. cognitive function.tw.
29. ((clinical or physiological or psychological) and assessment$).tw.

30. abnormalit$.tw.
31. impair$.tw.
32. exp Infection/
33. susceptibility to infection$.tw.
34. exp treatment outcome/
35. Treatment outcome$.tw.
36. Cost-Benefit Analysis/
37. (cost$ and benefit$).tw.
38. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 8 and 12 and 22 and 38

This was then limited by year (2000 to January 2010).

RESULTS: The above strategy retrieved 1074 citations from Medline. A similar search was conducted in Embase, the Cochrane Library, CRD databases, PsycINFO, Cinahl and Web of Science.

Database	Number of references
Medline	1074
Embase	1263
Cochrane Library	215
CRD databases	94
PsycINFO	37
Cinahl	318
Web of Science	1889
Total	**4890**

There was some duplication of references between different database searches.

The titles and abstracts of these citations were scanned for relevance to screening for iron deficiency anaemia in children, aged under five (preschool). In particular, the following issues were highlighted as important:

- **The condition** – how is iron deficiency anaemia defined, what measures do you use and at what point is a child considered to be iron deficient? Does it matter if you don't screen?
- **The test** – what test should be used?
- **The treatment** – what is the treatment? Is it acceptable, what are the harms and benefits of the treatment? (The treatment)
- **The screening programme**

230 citations were deemed to be relevant.

The above searches were run again on 28 October 2011.

The following results were retrieved.

Database	Number of references
Medline	230
Embase	563
Cochrane Library	45
PsycINFO	20
Cinahl	42
Web of Science	485
Total	**1390**

After duplicates were removed, **963** references remained. The titles and abstracts of these citations were scanned for relevance as detailed above. **63** citations were deemed to be relevant.

Therefore, in total, **293** citations were passed to the expert reviewer for further sifting and appraisal for inclusion in the review.

Quality

Publications published since 2006 were focussed on, since this was the date of the last policy review. The full text of selected papers was retrieved after a first pass appraisal at abstract level. Guidelines, systematic reviews and studies from the UK, Europe and the US were prioritised. Foreign language papers were excluded. For treatment and prevention sections, studies performed in developing countries were excluded. Additional relevant references identified during the preparation of the report were also included.

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