UK National Screening Committee

Screening for elevated blood lead levels in asymptomatic children aged 1 to 5 years

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

Version: Final

Bazian Ltd.

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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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Abbreviations List

aOR – Adjusted odds ratio

AUC – Area under the curve

BLL – Blood lead level

CDC – Centers for Disease Control and Prevention

CI – Confidence interval

DD – Developmental delay

FN – False negative

FP – False positive

LD – Learning difficulty

NPV – Negative predictive value

OR – Odds ratio

PPV – Positive predictive value

RCT – Randomised controlled trial

SR – Systematic review

TN – True negative

TP - True positive

Plain English Summary

Condition

Lead poisoning is a serious health hazard that can lead to severe health problems, especially in young children.[1] Lead is naturally present in the environment in small amounts in rock, water, soil dust and air. There are a number of other potential sources of lead in the environment, including industry, leaded petrol, older paint, water piping and hobbies that use lead.[1] At high levels, lead poisoning in children can cause anaemia, damage to internal organs, seizures, coma and death. There has been concern that low levels of lead within the environment are causing a number of problems, including developmental and behavioural conditions.[1]

Children are at higher risk of lead poisoning as they often place objects in their mouths. Lead is stored in the body and can remain in the bone for a number of years, meaning that it could be released into the blood many years after exposure. Lead is gradually expelled from the body through urine.

Treatment

Chelation agents are available to treat children with elevated blood lead levels. These drugs are injected into the bloodstream where they bind to the lead and allow it to pass through the kidneys and be removed through the urine. Treatment is mainly reserved for children with high blood lead levels in order to reduce the risk of death from severe brain injury. These drugs cannot remove the lead stored in bone or reverse nerve damage or less severe brain problems.[1]

Screening and previous/Current UK NSC Recommendations

The most recent UK National Screening Committee (UK NSC) external review of elevated blood lead, published in 2013, concluded that universal screening for all children without symptoms aged 1 to 5 years should not be recommended.

Based on the UK NSC criteria, screening was not recommended in the 2013 review because:

- the prevalence of elevated blood lead levels is low
- there are ways of stopping children getting raised blood levels in the first place
- the test misses lots of children with raised blood lead levels
- the evidence does not say what level of blood lead should be treated
- there is no treatment for the majority of cases (very low levels of raised blood lead levels) that would be identified by screening
- there is no research comparing screening with usual methods of identifying and treating children in the UK

Findings

This review could not find any new evidence about:

- the number of children with raised blood levels in the UK
- an acceptable screening test
- how well treatment works in children identified through screening

Recommendation

The UK NSC does not recommend screening all children aged 1 to 5 years old for elevated blood lead levels.

Executive Summary

Background

Lead toxicity is a serious health hazard that can lead to severe health problems, especially in young children.[1] At high levels, lead toxicity in children can cause anaemia, multi-organ damage, renal damage, seizures, coma and death. Concern has now grown regarding chronic low level of lead exposure within the environment. This is because even at low levels, lead can be toxic and it can cause a number of problems in children, including cognitive, psychological and neurobehavioral impairment.[1]

Lead is naturally present in the environment in small amounts in rock, water, soil dust and air. There are a number of other potential sources of lead in the environment, including food, industry, leaded petrol, older paint, lead water piping, smoking and hobbies that use lead.[1, 2] Young children often place objects in their mouths resulting in lead-contaminated dust and soil ingestion and are more vulnerable as they take in relatively more toxins from the environment than adults. The higher risk of lead toxicity is due to their increased intake of lead per unit of body weight compared with adults and their higher rate of physiological uptake. The harmful effects of lead in the body can be experienced in every organ system, but particularly the nervous system, which can affect developmental processes in children. Lead is stored mostly in blood, soft tissue and bone, and can remain in the bone for years, so might be transferred back into the blood long after initial exposure. Lead is gradually expelled from the body through urine.

Purpose/aim of the review

This review assessed whether screening for elevated blood lead levels (BLLs) should be recommended for asymptomatic children aged 1 to 5 years. The review considers literature published between January 2012, the date of the evidence search for the last UK NSC review, and March 2017.

Previous/Current UK NSC Review

The UK NSC currently recommends against universal screening for elevated blood levels in all children aged 1 to 5 years old. This followed the previous external review published in 2013, which highlighted several key uncertainties including a low prevalence of raised lead levels in the blood, benefits from primary prevention, no reliable screening strategies and a lack of proven treatment for those children identified through screening.

Findings and gaps in the evidence

The current review found a lack of new evidence:

1. No new studies report the prevalence of elevated BLLs in the UK population being considered for screening (asymptomatic children aged 1 to 5).

2. There was little evidence on the acceptability of non-invasive screening methods. Venous blood samples provide accurate assessment of BLLs, but non-invasive methods such as questionnaires are likely to be a more acceptable form of universal screening in children. Few studies describing the accuracy of non-invasive screening tests have been published since the last review. One systematic review and one additional cross sectional study were identified. Both studies suggest that screening questionnaires perform little better than average for detecting children with elevated BLL. The review had several limitations including searching restricted to only one literature database and giving limited information on study quality or child eligibility criteria. As such it is not known if these were nationally or regionally representative child samples. The cross sectional study tested a reduced version of a screening questionnaire being used in France at that time. Not all questions were included, and there was over-representation of high risk children. This may not give an accurate indication of screening test performance in the general population.

3. No new studies had assessed the benefit of treatment in children with raised blood lead levels (≥10µg/dL to ≥45µg/dL).

Recommendations on screening that can be made on the basis of the current review

The UK NSC does not recommend universal screening of all children aged 1 to 5 years old for elevated blood lead.

Introduction

Lead toxicity is a serious health hazard that can lead to severe health problems, especially in children.[1] At high levels, lead toxicity in children can cause anaemia, multi-organ damage, renal damage, seizures, coma and death. At low levels, lead can also be toxic, causing a number of problems in children, including cognitive, psychological and neurobehavioral impairment.[1]

Lead is naturally present in the environment in small amounts in rock, water, soil dust and air. There are a number of other potential sources of lead in the environment, including food, industry, leaded petrol, older paint, smoking or second hand smoke, lead water piping and hobbies that use lead.[1, 2]

Young children often place objects in their mouths resulting in lead-contaminated dust and soil ingestion and are more vulnerable as they take in relatively more toxins from the environment than adults. This higher risk of lead toxicity is due to their increased intake of lead per unit of body weight compared with adults and their higher rate of physiological uptake. The harmful effects of lead in the body can be experienced in every organ system, particularly the nervous system, which can affect developmental processes in children. Lead is stored mostly in blood, soft tissue and bone, and can remain in the bone for years after initial exposure, and might be transferred back into the blood long after this time. Lead is gradually expelled from the body through urine.

Since the early 1980s the World Health Organization and the International Programme on Chemical Safety have been concerned about the importance of lead toxicity as a major environmental hazard,* leading to an international call for the reduction of lead in the environment. Primary prevention measures, such as banning lead in petrol[3] and the replacement of lead piping,[4] have been introduced in many countries including the UK resulting in the reduction of the risk of lead exposure in recent years.[5] General sale of paint containing lead has also been banned in the UK since 1992.[2]

However, lead toxicity remains a major health concern especially in children where recent evidence has shown that there is no safe level of BLL. The Centers for Disease Control in the USA currently recommend a BLL of 5 µg/ dL to be used as a threshold for initiating educational programmes, environmental investigations, and medical monitoring.[6] According to the World Health Organization a BLL of 10 µg/ dL is the level that may cause neuro-cognitive effects in children.[7]

Lower socioeconomic status has been found in some studies to be a risk factor for elevated BLLs.[8, 9] This may in part be due to increased likelihood of residence in an area with lead industry, or renovation or deterioration of older houses containing lead-based paint.

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* http://apps.who.int/iris/browse?type=author&value=WHO+Task+Group+on+Environmental+Health+Criteria+for+Lead%3A+Environmental+Aspects

Chelation therapy is the main treatment used for children with BLLs greater than 45.0 µg/ dL. This reduces the risk of death due to severe acute lead encephalopathy, although the lead sequestered in bone cannot be removed, and neuropsychological effects cannot be reversed.[1]

Basis for current recommendation

The most recent UK NSC external review of elevated blood lead, published in 2013, concluded that asymptomatic children aged 1 to 5 years should not be screened.

Based on the NSC criteria, screening was not recommended because:

1. The prevalence of elevated BLLs is low. The number of people affected has been in decline for many years, due to primary prevention measures, and so very few children in the UK were thought to be affected. There was, however, no recent data on the prevalence of raised BLLs in the UK.
2. Current screening strategies lacked reliability. Capillary testing had low sensitivity and specificity, mainly due to the chance of contamination via equipment and the skin. Where screening questionnaires had been used, they were found to be no better than chance at identifying elevated BLLs.
3. There was a lack of a suitable cut-off for screening as there is no "safe" BLL.
4. There was a lack of proven treatment for those asymptomatic children likely to be identified through screening, with raised blood levels ≥ 10µg/dL to ≤ 45µg/dL (that is, at levels below the threshold at which chelation therapy is recommended)

The review suggested that "consideration should be given to the introduction and implementation of a comprehensive, co-ordinated primary prevention strategy for raised BLLs in the UK."

Current update review

The current review was prepared by Bazian Ltd., and then reviewed and revised as needed in discussion with the UK National Screening Committee evidence team. The review considers whether the volume and direction of the evidence produced between 2012 and 2017 indicates that the previous recommendation should be reconsidered.

Three main criteria will be considered, with particular focus given to areas the 2013 review identified as uncertain, or supported by insufficient evidence. The main criteria and key questions reviewed are:

Table 1. Key questions for current elevated blood lead update review

Criterion	Key Questions (KQ)	# KQ Studies Included
1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and	What is the prevalence/incidence of elevated BLLs in children aged 1-5 years in the UK?	5

natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.		
4. There should be a simple, safe, precise and validated screening test.	What is the accuracy of non-invasive screening tests for the detection of elevated BLLs in children aged 1-5 years?	2
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.	What are the benefits/harms of treating children with lower elevated blood levels (≥ 10µg/dL to ≤ 45µg/dL)?	0

The key questions were derived from the 2013 external review and through discussion with UK NSC evidence team members and members of the UK NSC. Discussion between Bazian Ltd and the UK NSC evidence team further developed the questions and provided information required for developing the search strategy**.**

Table 2 describes the study eligibility criteria for each key question by population, intervention, comparator and outcome (PICO), as applicable. These were decided *a priori* at the scoping stage.

A systematic literature search of 3 databases was performed for studies published between 1 January 2012 and 3 February 2017. The search strategy is detailed in the Appendix.

Overall the search yielded 1,571 references addressing elevated blood lead. Of these, 248 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 35 were selected for appraisal at full text.

Selection and appraisal of studies was predominantly undertaken by one reviewer, though any queries were resolved by discussion with a second reviewer, or with the UK NSC evidence team. Any refinements to the inclusion criteria as outlined in Table 2, and further information on the evidence selection process for each key question, is discussed in the evidence description for each criterion.

Each criterion was summarised as ‘met’, ‘not met’ or ‘uncertain’ by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section, as well as the comment section of the Appendix tables.

For Criterion 4, quality assessment was performed using a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). This focused on 4 main domains: patient selection, the index test, the reference standard, and flow and timing of index test and reference standard. Each domain was assessed for risk of bias, and the first 3 domains were assessed for applicability to a potential UK screening programme population. Details of these assessments can be found in the comment section of the Appendix tables. For other studies informal quality assessment was performed, that is, without the use of a formal tool. This assessment considered the risk of bias in each study relating to its methodology, for example, how the study sample was selected for studies of prevalence, and also applicability to the UK setting.

The review was checked in accordance with Bazian Ltd’s quality assurance process.

Table 2. Study inclusion and exclusion criteria by key question

Key question	Inclusion criteria					Exclusion criteria
	Population	**Intervention**	**Comparator or reference standard**	**Outcome**	**Study type**	
1) Incidence	Children aged 1-5 years	NA	NA	Elevated BLLs reported by the following ranges •<10µg/dL •≥10 to ≤45µg/dL •>45µg/dL	UK should be prioritised; other studies carried out in Western populations that are analogous to the UK can also be included. Observational studies eg, cross sectional studies or cohorts, registry data and systematic reviews (SRs) of these Studies should be representative of the general child population and with sample size >500; incidence/prevalence within specific groups (eg, sociodemographic) would also be considered.	Reports from countries not generalisable to the UK
2) Screening test	Children aged 1-5 years	Identification of elevated BLLs by •Questionnaire •Other possible, non-invasive test	Identification of elevated BLLs by •Venous sample	Test accuracy/validity outcomes •Sensitivity and specificity •PPV and NPV •Likelihood ratios (+/-) Reported for the 3 ranges reported above	Ideally, studies carried out within the UK should be prioritised; other studies carried out in Western populations that are analogous to the UK can also be included. Diagnostic accuracy studies with performance data available (eg, cohorts were the full sample has received the index and reference test) and SRs of these studies. Studies should be conducted in non-selected samples (eg, consecutively enrolled).	Studies reporting on screening populations outside of this age range.
3) Treatment	Children aged 1-5 years with elevated BLLs of ≥ 10µg/dL to ≤ 45µg/dL Ideally screen detected, otherwise clinically detected	•Chelation therapy •Nutritional interventions (eg,calcium, zinc, vitamin C or D) •Removal of lead from the environment •Removal of children from the contaminated environment	•No treatment •Placebo •Possibly alternative intervention	•Reduction in BLLs •Cognitive improvement •Improved neurobehavioural outcomes •Adverse effects of treatment Reported by range of elevated level as above	Ideally, studies carried out within the UK should be prioritised; other studies carried out in Western populations that are analogous to the UK can also be included. RCTs prioritised or alternatively comparative cohorts or SRs of these studies Ideally screen detected, otherwise clinically detected	Reports from countries not generalisable to the UK

NA not applicable

Appraisal against UK NSC Criteria

These criteria are available online at. https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes

1. **The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.**

The consequences of lead toxicity are serious and in children can result in cognitive, psychological and neurobehavioral impairment.[1] Children are at higher risk due to their intake per unit of bodyweight and higher rate of physiological uptake. In 1991, the Centers for Disease Control and Prevention (CDC) defined BLLs of 10.0 µg/dL (100 µg/L) or more as a "BLL of concern" for children aged one to five years.

In the last decade a large body of evidence has emerged in relation to children's exposure to lead such that BLLs that were previously considered safe are now recognised to cause serious health issues, even in the absence of overt symptoms. This led to a decrease in the recommended BLL in children from ≤10 µg/dL to ≤5 µg/dl.[10]

The 2013 UK NSC evidence review did not address this criterion in detail; however, the report stated "*Lead has a detrimental effect on health of children even at very low blood levels. The exact level of health risk at this low level is not known. Cases at higher blood levels in the UK are very much reduced meaning it is unlikely to be a major health problem. However, the lack of robust surveillance data means that in the UK it is not possible to confirm accurately the size of the problem and especially in relation to the impact of blood lead levels below 5µg/dL on very young children in their developmental years*."

Current UK NSC key question

The current evidence summary aims to establish whether elevated BLLs in children aged 1 to 5 years is an important health problem, looking at the prevalence and incidence in the UK or comparable settings.

Description of the evidence

Overall, 20 studies were identified as potentially relevant during title and abstract sifting and were further assessed at full text. UK studies were prioritised with other studies from Western populations that are comparable to those in the UK. Studies eligible for inclusion were observational, cross-sectional, cohort studies, registry data and systematic reviews. Ideally the study should have included a sample of 500 children or more and be representative of the general population, though studies reporting the incidence or prevalence in specific populations were also considered.

Of the 20 studies assessed, 5 were included in the final analysis. The main reasons for exclusion were studies conducted in non-comparable populations, for example children in China, or that included a small number of children.

One UK study was identified, but this was available as an abstract only. Full details of the methods were not available and the research would not have undergone full peer review.[11] Most importantly, it analysed a small sample of children (n=104) with unexplained developmental delay and learning difficulties (in whom elevated lead levels may be more common), so is not representative of the wider general population or of asymptomatic children. Therefore it was excluded from the analysis.

Results

Five studies were included: one from France[12] and four from the US.[8, 13-15] These studies are summarised in table 3 below.

Table 3. Results of studies looking at prevalence of raised blood lead levels

Study country, region, years	Participant number, ages, description	Prevalence of blood lead≥5 µg/dL	Prevalence of blood lead ≥10 µg/dL	Average BLLs (µg/dL)
Tsoi et al (2016)[15] US, 1999 to 2014 (Appendix 5)	6,684 children aged 1-5 years old in a nationally representative survey	1999-2000: 9.9% 2013-2014: 0.5% (estimated)	NR	1999-2000: 2.14 for boys, 2.37 for girls 2013-2014: 0.81 for boys, 0.75 for girls (estimated)
McClure et al (2016)[8] US, 50 states plus District of Columbia, 2009-2015 (Appendix 4)	3.8 million children, aged <6 years	2.95% **2009-10:** 3.67% **2014-15:** 2.59%	0.58% **2009-10:** 0.74% **2014-15:** 0.55%	NR
Kennedy et al (2014)[14] US, New York State (excluding New York City) and Monroe County, 1997-2011 (Appendix 3)	Children (number not reported) <6 years, data identified in laboratory surveillance	NR for US or NY State Displayed graphically for Monroe County: Peaked at 40% in 1995, declined to about 5% in 2012	**1997:** Monroe County: 13.4% New York State: 6.3% US: 7.6% **2011:** Monroe County: 1.1% New York State: 1% US: 0.6%	NR
Jackson et al (2012)[13] US, Evansville, Indiana, 1998 to 2006 (Appendix 2)	11,719 children aged 1-5 years, having voluntary testing	52.8% (≥6 but <10 µg/dL) 56.7% (≥6 µg/dL)	3.9% (1.8% confirmed) **1998:** 8.0% **2006:** 3.1%	3.0 (median)
Etchevers et al (2014)[12] France, 2008-2009 (Appendix 1)	3,831 aged 1-6 years attending 143 hospitals in France	1.5%	0.09%	1.49

Abbreviations: DD, developmental delay; LD, learning difficulty; NR, not reported. NB: Studies did not all report BLL in µg/dL; results have been converted to this unit in this table for ease of comparison. Original figures are reported in the study extractions in the Appendices.

In France, a cross-sectional survey included 3,831 children aged between 6 months and 6 years between 2008 and 2009.[12] Children were recruited from 143 hospitals predominantly in areas

with high risk of lead pollution. Samples were weighted by age, gender, region and eligibility for health insurance to try and obtain prevalence estimates that could be generalised to children in France as a whole. However, it is uncertain how representative these estimates may be given that children were hospitalised and from mostly high-risk regions. The mean BLL was 1.49 µg/dL, with 0.09% of children having a BLL ≥10 µg/dL and 1.5% a BLL ≥5 µg/dL. Further to this an environmental investigation was carried out in children with high BLL (>10 µg/dL). Possible sources of exposure were polluted soil, cosmetics, leaded paint, dust or use of traditional cookware.

Several similar studies have been carried out in the US.[8, 13-15] All of these studies included children aged less than 6 years. Overall they suggested that BLLs in young children have been decreasing in the US in recent years.

One of the two most recent studies used a nationally representative sample of participants to estimate blood lead levels for the entire population of the USA between 1999 and 2014.[15] It included 6,684 children aged 1 to 5 years old (as well as participants of other ages). Different participants were assessed in each year. It estimated that the proportion of children with BLLs ≥5.0 mg/dL decreased from 9.9% in 1999-2000 to 0.5% in 2013-2014. (It did not assess the prevalence of BLLs ≥10.0 mg/dL).

Given that extent of lead exposure is likely to be geographically variable (for example due to varying proximity to industrial sites which may produce lead), it is possible that the sample taken in this survey (about 800 children per year) was not large enough to truly capture this variability. However, it was the only US study to attempt to make its figures nationally representative, and not to rely on self-selection of participants.

The study which reported measuring levels in the most children was a 6-year retrospective study looking at BLLs in 3.8 million children, taken by venous testing, between 2009 and 2015 from all 50 states of the US and the District of Columbia.[8] Results were from a large national clinical laboratory database, from a private laboratory provider.

The overall prevalence of BLL ≥5.0 mg/dL was 2.95% and for BLL ≥10.0 mg/dL was 0.58%. However, prevalence fell over the study period, from 3.67% in 2009-10 to 2.59% in 2014-15 for BLL ≥5.0 µg/dL, and from 0.74% to 0.55% for BLL ≥10.0 µg/dL. The decline was reported to be across most demographic groups, and as a result of public health initiatives. Other factors associated with elevated BLL included male gender and lower socioeconomic status.

Another US study analysed laboratory surveillance data from 1997 to 2011 to establish the rate of confirmed elevated BLL (≥10.0 µg/dL) in New York State (excluding New York City) and Monroe County, as well as the US as a whole.[14] During the study period the prevalence of elevated BLL decreased in all of the regions assessed. The overall US data came from the CDC, and the rate of elevated BLL in 2011 (0.6%) was similar to that reported for 2015 in the McClure study (0.6%).

This study did not provide overall data on the rate of BLLs ≥ 5 µg/dL but did show these for Monroe County, where rates dropped from a peak of 40% in 1995 to about 5% in 2012.

The study did not state how many child samples were analysed for each region. The rates of BLL testing were only shown for Monroe County where they were about 25% in 2012, which was reported to be higher than the US as a whole. Therefore the prevalence rates identified may not

be representative of the general population, particularly if those tested are self-selecting or being targeted due to high risk.

A study conducted in Evansville, Indiana, looked at BLL in children aged 1 to 5 years presenting for voluntary testing between 1998 and 2006.[13] A very high proportion of children in this study had BLL between 5 and 10 µg/dL (52.8%), and 3.9% had BLL ≥ 10 µg/dL. These high levels may have been due to the town having industrial soil contamination with lead, and a large number of older houses (which probably had lead paint). The sample may also have self-selected due to concerns about lead exposure. Therefore this study is unlikely to be representative of less industrial areas, or areas with newer housing. The authors note that levels were higher than US national averages, and BLLs decreased over the period of study.

Summary: Criterion 1 not met

The volume of relevant studies published since the last UK NSC evidence summary is small. No new studies have described the prevalence of elevated BLL in the UK population being considered for screening (asymptomatic children aged 1 to 5). Therefore UK prevalence is still unknown.

This evidence summary includes four studies from the US and one study from France describing the burden of elevated BLLs in young children. The studies from the US suggest that the prevalence of BLL ≥5 or 10 µg/dL has decreased over the past decades. The most recent study reported on a survey which aimed to be nationally representative. It estimated that in the US as a whole, the proportion of children aged 1 to 5 years old with BLLs ≥5 µg/dL decreased from 9.9% in 1999-2000 to 0.5% in 2013-2014. It is possible that this survey may not have been large enough to fully capture geographic variability in BLL levels, but it was the most robust US study identified.

The other three US studies had the potential for selection bias, as participants were self-selecting and may have been targeted for testing due to high risk of elevated BLL. All three of these studies reported higher proportions of raised BLLs than the nationally representative survey. The largest of these studies (which assessed 3.8 million samples) reported BLLs in 2014-2015 of 2.59% for BLL ≥5.0 µg/dL, and 0.55% for BLL ≥10.0 µg/dL

A French cross sectional study from 2008-9 found rates of 0.09% of children having BLL ≥10 µg/dL and 1.5% with BLL ≥5 µg/dL. This study aimed to be nationally representative but over-selected children at high risk.

It is difficult to be certain to what extent other countries will have rates of elevated BLLs similar to those in the UK. This is due to the potential for differences between countries in exposure to risk factors e.g. variation in when lead paint or leaded petrol was banned, differing proportions of housing with older lead-containing paint, and differing levels of industrial exposure.

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

Description of the previous UK NSC evidence review conclusion

The previous UK NSC review reported that present screening tests have limitations, especially as prevalence levels fall below 10µg/dL.[16] The most commonly used screening test for BLL is the capillary test though this has been found to have a high false positive rate compared to venous sampling.[17] The poor accuracy may be due to environmental lead contamination on the skin or equipment during collection, and also the day to day biological variability in BLL which leads to a different result at later venous testing.

Current UK NSC key question

The current evidence summary looks into the accuracy of non-invasive screening tests for the detection of elevated BLL in children aged 1 to 5 years.

Non-invasive methods were of interest as they are likely to be a more acceptable form of universal screening in young children. A venous blood sample would give an accurate result but is less likely to be practical or feasible (though the last UK NSC review found limited evidence on the acceptability of lead screening).

Description of the evidence

Overall, 11 studies were identified as potentially relevant during title and abstract sifting and further assessed at full text. UK studies were prioritised with other studies from Western populations that are comparable to those in the UK. Diagnostic accuracy studies with performance data available (for example, in cohorts where the full sample has received the index and reference test) were eligible for inclusion, along with SRs of these studies. Studies ideally needed to be conducted in non-selected population samples (for example, consecutively enrolled), though some revision was made to this inclusion criteria has mentioned below.

Of the 11 studies assessed, 2 were included in the final analysis. The main reasons for exclusion were studies conducted in populations not comparable to the UK, inappropriate study design or the full sample not receiving both the index and reference test. The only other potentially relevant study of a non-invasive screening test identified by the search was a saliva test. However, this was excluded as it was conducted in a non-representative population of children living in an area known to be lead-contaminated in Thailand.

Two other studies from the US were identified that discussed the use of questionnaires in screening; however these did not provide any test performance data (such as sensitivity or specificity for detection of BLL above a given threshold) and were therefore excluded. One study looked at whether children with detectable BLL (≥3.3 µg/dL) were more likely to have positive responses on certain screening questionnaire items than not. The other assessed whether BLLs were significantly higher in children who screened positive on a verbal screening questionnaire.

One systematic review[18] and one cross sectional study[19] were selected for inclusion. Both the SR and cross sectional study used questionnaires as screening tools and included questions on socioeconomic status, the child habits and any potential symptoms.

The systematic review was mentioned in the previous external review for the UK NSC, but was published after the 2012 search date of that review and therefore fell within the search date of the current review. The cross sectional study was the same population sample (though different study report) as the study by Etchevers et al included for criterion 1.[12]

Both studies were included with the caveat that they did not include completely non-consecutive, population samples and may give uncertain national or regional representation. For example, the studies included by the SR had variable setting, with some reported to be

community-based but the majority conducted in paediatric clinics. The cross sectional study was hospital-based and preferentially included hospitals from regions in France where lead contamination was thought to be higher. However, these 2 studies were included as the best evidence available for this question.

A summary of the results of these studies is presented in table 4 below.

Results

Table 4: Blood lead level screening by non-invasive methods

Study	Population characteristics	Screen test/ Reference test	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
Ossiander (2013)[18] Systematic review Search date: Up to Nov 2009. (Appendix6)	20 articles met inclusion criteria: including 28 separate questionnaire evaluations. Variable study settings, all US-based. Sample size range 131-9603.	Screening questionnaires/ blood test To detect lead poisoning (10 µg/dL or more)	**1991 CDC questionnaire** (17 studies) Pooled mean estimate 0.61 (0.53 to 0.68) **All other questionnaires** (11 studies) Pooled mean estimate 0.76 (0.68to 0.85	**1991 CDC questionnaire** (17 studies) Pooled mean estimate 0.52 (0.45 to 0.60) **All other questionnaires** (11 studies) Pooled mean estimate 0.41 (0.33to 0.49)	NR	NR
Etchevers et al (2015)[19] Cross sectional study (Appendix 7)	n=3,831 children from 143 paediatric hospital clinics in France or French regions overseas assessed 2008-09.	A questionnaire collecting socioeconomic, behavioural and environmental factors was administered by paediatricians and nurses at the hospitals, along with a blood test. Answers were collected from parents before they received the results of the blood lead test/Blood test To detect BLL > 5 µg/dL	0.51 (0.26 to 0.75)	0.66 (0.62 to 0.70)	NR	NR

The Ossiander systematic review evaluated the ability of lead screening questionnaires to predict lead poisoning risk among children.[18] Lead poisoning was defined as BLL ≥10 µg/dL.

This review included articles reporting the evaluation of predesigned questionnaires. Twenty articles met the inclusion criteria including 28 separate questionnaire evaluations, 17 of these were for the 1991 Centers for Disease Control and Prevention (CDC) questionnaire. The author did not use a specific tool to assess the quality of the included studies, therefore reliability is uncertain. Only a single line was given on the setting of each included study; some were community-based studies but most were paediatric clinics in states across the US. Inclusion

criteria for these studies are not given, and it is not known whether BLLs would be representative of the general population of young children in these regions.

The author also noted that many of the articles did not report on sensitivity or specificity, and those that did rarely provided confidence intervals, or assessed the predictive ability of the questionnaire compared to chance. Another limitation of the review is that it searched only one database which reduces confidence that all relevant studies prior to the 2009 search date were identified.

The review found that lead screening questionnaires had wide ranging sensitivity and specificity. The pooled mean estimates for the 1991 CDC questionnaire gave sensitivity of 61% and specificity of 52%, and for the other questionnaires was slightly higher at 76% and 41%, respectively. The review also calculated accuracy, as a sum of sensitivity and specificity. They stated that a test that received a sum of only 100% (maximum possible would be 200%) would be performing only as well as chance. The authors estimated the sum for the 1991 CDC questionnaire at 112% (95% CI 1.06 to 1.18), and for the other questionnaires was 113% (95% CI 1.06 to 1.20). Therefore the authors concluded that questionnaires performed "little better than chance" at identifying those who should go on to have blood testing.

A subsequent large cross-sectional survey from 2008-9 evaluated the performance of a screening questionnaire in identifying BLLs higher than 5 µg/dL among children receiving care at 143 hospitals across France or French regions.[19]

Hospitals were stratified by region and risk of lead poisoning according to factors such as prevalence of old housing and industrial pollution, and those in high-risk regions were intentionally oversampled. Sample weighting by region, gender, age and eligibility for health insurance was then used to give nationally representative estimates. However, it cannot be known with certainty that the data would represent all young children in France.

The study was also unable to assess all of the current screening questions; therefore results may not be fully representative of its true performance. Children whose parents responded "don't know" to any of the questions were excluded from the main analysis, which may have been inappropriate if they had any other questions where a risk factor had been identified. However, when these individuals were considered as screen positives this did not change results to a great extent.

The results showed that the screening questionnaire had low sensitivity (51%) so would miss almost half of those with BLL levels >5 µg/dL. Screening questionnaire performance was little between than chance with an area under the curve (AUC) of 0.76 and a sum of sensitivity and specificity of 117%.

Etchevers et al suggested that the screening questionnaire could be updated with additional criteria such as parental smoking, housing occupancy, and residence in a municipality or census block where a high proportion of housing is substandard and built pre-1949. Adding these criteria improved questionnaire performance to give an AUC of 0.86. It was estimated that at best sensitivity would be 96% and specificity 55%, giving an accuracy sum of 151%.

Summary: Criterion 4 not met

Few additional studies describing the accuracy of non-invasive screening tests for the detection of elevated BLLs have been published since the last UK NSC review. One systematic review reported that screening questionnaires vary widely in their sensitivity and specificity for detecting BLL ≥10 µg/dL, and generally perform poorly at predicting which children are at

greatest risk. There were some limitations to this review, including literature searching restricted to only one database and lack of information on study quality or child eligibility criteria.

Only one additional cross sectional study provided information about screening questionnaire accuracy. This also found the questionnaire to have low sensitivity – with the test missing almost half of those with BLLs >5 µg/dL. The questionnaire tested in this study was the one being used in France for screening at that time; however, not all questions were included. The study is also likely to be over-representative of high risk children. Therefore, the results may not represent screening test performance in the general population.

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.

Description of the previous UK NSC evidence review conclusion

The previous UK NSC review states "Chelation is not advised for BLLs less than 45 µg/dL. It is this level that would be mainly identified in a screening programme. For children identified at the lower level removal from the source of lead is advised and primary prevention interventions to remove the source long term."

Current UK NSC key question

The current evidence summary aims to establish the benefits/harms of treating children with lower elevated blood levels (≥ 10µg/dL to ≤ 45µg/dL).

Description of the evidence

Overall, 4 studies were identified as potentially relevant during the title and abstract sifting and further assessed at full text. UK studies were prioritised, along with other studies from Western populations that are comparable to those in the UK. Studies eligible for inclusion were RCTs, but in the absence of these comparative cohorts, or SRs of these studies. Studies in children whose elevated lead levels were screen detected were prioritised, but in the absence of these studies in children with clinically detected.

Of the 4 studies assessed at full text, no studies were suitable for inclusion in the final analysis. Some of the reasons for exclusions were that the population did not have elevated BLL (≥ 10µg/dL), the age of included participants was a mixture of children and adults, and inclusion in the previous NSC review.

Summary: Criterion 9 not met

No studies were identified that assessed interventions for reducing levels of blood lead in lead-exposed children.

Conclusions

Implications for policy

This report assesses screening for elevated BLLs in children aged 1 to 5 years against selected UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

This review assessed key questions to determine if evidence published since 2012 supports a change to the recommendation on screening for elevated BLLs in the UK. Limited evidence on the benefits and harms of treating children with elevated BLLs, and the accuracy of non-invasive screening tests was identified.

The volume, quality and direction of evidence published since 2012 does not indicate that screening for elevated BLLs should be recommended in the UK. Several uncertainties remain across key criteria, including:

- lack of evidence that elevated BLLs in children is an important health problem in terms of UK prevalence
- lack of evidence on accuracy of non-invasive screening tests for the detection of elevated BLLs. No optimum screening strategy could be identified
- lack of evidence of a benefit or harm of treating children with lower elevated BLLs

Limitations of the rapid review process

This rapid review process was conducted over a condensed period of time (12 weeks). We limited our searching to 3 bibliographic databases and did not search grey literature sources. Literature search and first pass appraisal were predominantly undertaken by one information specialist, and second pass appraisal and study selection by one analyst, though any queries at both stages were resolved through discussion with other reviewers, or with the UK NSC. Similarly any revisions to the inclusion or exclusion criteria were made following discussion.

Systematic reviews were prioritised during the appraisal, before sifting through the lower hierarchy of evidence.

Studies available only in non-English language, abstracts, conference reports or poster presentations were not included. Study authors were not contacted and studies that were not published in peer-reviewed journals were not reviewed.

Methodology

The draft update report was prepared by Bazian Ltd., and then adapted in discussion with the National Screening Committee. Each criterion was summarised as ‘met’, ‘not met’ or ‘uncertain’ by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were assessed to determine the quality of the identified

evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables.

Search strategy

Medline and Embase (Embase.com)

#1 'lead poisoning'/de
#2 'lead blood level'/de
#3 (lead NEAR/2 poison*):ab,ti
#4 (lead NEAR/2 (blood OR plasma OR serum)):ab,ti
#5 (lead NEAR/2 (intoxication OR toxicity OR injest* OR ingest* OR absorb*)):ab,ti
#6 (lead NEAR/2 (hazard* OR induc* OR exposure)):ab,ti
#7 'lead'/de
#8 hazard*:ab,ti OR expos*:ab,ti OR neurotoxic*:ab,ti OR environ*:ab,ti
#9 'environmental exposure'/mj
#10 #8 OR #9
#11 #7 AND #10
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #11
#13 child*:ab,ti OR baby:ab,ti OR babies:ab,ti OR infant*:ab,ti OR toddler*:ab,ti OR 'pre school':ab,ti OR preschool:ab,ti
#14 #12 AND ([child]/lim OR [infant]/lim OR [preschool]/lim)
#15 #12 AND #13
#16 #14 OR #15
#17 #14 OR #15 AND [2012-2017]/py

Cochrane Library (CDSR, CENTRAL, HTA, NHS EED, DARE)

#1 MeSH descriptor: [Lead Poisoning] explode all trees
#2 MeSH descriptor: [Lead Poisoning, Nervous System] explode all trees
#3 MeSH descriptor: [Lead] this term only
#4 (lead near/2 (poison* or blood or plasma or serum)):ti,ab,kw
#5 (lead near/2 (toxicity or neurotoxic* or intoxic* or exposure)):ti,ab,kw
#6 (lead near/2 (hazard* or induc* or injest* or ingest* or absorb*)):ti,ab,kw
#7 #1 or #2 or #3 or #4 or #5 or #6
#7 #1 or #2 or #3 or #4 or #5 or #6 Publication Year from 2012 to 2017

Database	Number of references
Embase/Medline	1511
The Cochrane Library	60

248 citations were deemed to be relevant at first pass appraisal.

Appendices

Appendix number	1
Relevant criteria	1
Publication details	Etchevers A, Bretin P, Lecoffre C, Bidondo ML, Le Strat Y, Glorennec P, et al. Blood lead levels and risk factors in young children in France, 2008-2009. International journal of hygiene and environmental health. 2014;217(4-5):528-37.
Study details	Cross-sectional survey 2008-9, France. Children were recruited from 143 hospital paediatric departments in mainland France and French regions overseas, where the children were undergoing venous blood testing. Hospitals from regions where elevated BLLs were most likely, due to old housing and industrial pollution, were oversampled to obtain more precise estimates. Weighting of the sample was used to generate unbiased estimates of the entire population of the ages of interest in France.
Study objectives	To determine the BLL distributions in children between the age of 6 months and 6 years in France
Inclusions	Hospitalised children aged 6 months to 6 years who had had blood tests for medical reasons
Exclusions	Children with severe diseases or hospitalisation for chelating treatment or follow-up for lead poisoning
Population	n=3,831 **Age in years (%)** 0.5 to <1 = 576 (15.0%) 1 to 3 = 2,253 (58.8%) 4 to 6 = 1,002 (26.2%) **Child's country of birth (%)** France = 3,776 (98.6%) Other = 40 (1.0%) Data missing = 15 (0.4%) **Gender (%)** Male = 2,146 (56.0%) Female =1,685 (44.0%)

Results/outcomes	National geometric mean BLL was 14.9 µg/L (95% CI 14.5 to 15.4) Estimated national prevalence of BLL exceeding 100 µg/L (10 µg/dL) was 0.09% (95% CI 0.03 to 0.15) and 1.5% (95% CI 0.9 to 2.1) for ≥50 µg/L (5 µg/dL). The authors reported that in children between the ages of 1 and 6, levels of lead exposure have decreased over the past 15 years (BLL ≥10 µg/dL: 2.1% in 1996 vs. 0.09% in 2008-9). However, they estimated that in France there would still have been approximately 76,000 children with BLL (76,149) over the 5 µg/dL threshold based on their results.
Comments	The population sample was selective to over-represent hospitals from high-risk regions of France and its territories. Weighting of the sample by age, gender, region and eligibility for health insurance intended to give nationally representative figures. While use of only children who were already having a venous blood test in hospital made the study feasible, it is possible this may have biased the sample, although the authors felt the impact would have been minimal after their weighting.

Appendix number	2
Relevant criteria	1
Publication details	Jackson D, Grosse C, Zarus GM, Rosales-Guevara L. Higher blood lead levels among children living in older homes in Evansville Indiana: Associations between year house built, soil lead levels and blood lead levels among children aged 1-5 years-1998 to 2006. Revista de Salud Ambiental. 2012;12(1):34-45.
Study details	The Blood Lead Poisoning Prevention Program is administered through the Indiana State Department of Public Health and targets children less than 6 years old on a volunteer basis. Data was submitted by the state to the Centers for Disease Control and Prevention's (CDC's) Childhood Blood Lead Surveillance System. The CDC reports that testing is carried out using either capillary or venous blood and analysed by a Clinical Laboratory Improvement Amendments certified facility or with an approved portable instrument. Elevated BLL was defined as ≥10 µg/dL. This was considered as "confirmed" if the child had one venous blood specimen ≥10 µg/dL, or any combination of 2 capillary and/or unknown blood specimens ≥10 µg/dL drawn within 12 weeks of each other.
Study objectives	To identify trends in BLLs in children in Evansville, Indiana between 1998 and 2006, and to determine the association between BLLs and residential yard soil lead levels and year the house was built.
Inclusions	BLL testing was offered on a voluntary basis by the State of Indiana to children aged under 6 years. Therefore the group was a self-selected group who presented voluntarily for testing. Each child was only counted once in each year.
Exclusions	NR
Population	

	Percentage of total BLL samples	P-value
Sex		0.1012
Male	50.6	
Female	49.4	
Year house built		<0.0001
Before 1978	85.9	
1978 or later	14.1	
BLL test year		<0.0001
1998	12.5	
1999	13.0	
2000	12.6	
2001	13.2	

	<table><tr><td>2002</td><td>10.7</td></tr><tr><td>2003</td><td>11.2</td></tr><tr><td>2004</td><td>9.4</td></tr><tr><td>2005</td><td>9.5</td></tr><tr><td>2006</td><td>8.0</td></tr></table> A total of 18,218 BLLs were obtained from 11,719 children aged 1-5 years (total number of children in the region potentially eligible for testing not reported).
Results/outcomes	Evansville's BLLs were higher than national levels for the same age group (median BLLs in 2004-2006 of 3.0 vs 1.5 µg/dL for the US in 2001-02, respectively). Overall 3.9% of the children showed elevated BLL, (≥10 µg/dL) with only 1.8% having "confirmed" elevated BLL. In addition, over half of all children tested (52.8%) were reported to have BLLs equal to or above of 6 µg/dL but less than 10 µg/dL. During the study period 1998 to 2006, there was a decline in both median BLLs (6.0 µg/dL for the whole period vs. 3.0 µg/dL for 2004 to 2006) and the percentage of elevated BLLs. In 1998, 8.0% of children had elevated BLLs compared to 3.1% in 2006 (2.6% and 1.8% confirmed elevated respectively).
Comments	The study is relatively large but as the authors highlight, this was a convenience sample where participants self-selected to take part, and as such it may not represent all children living in Evansville. Participation may be biased towards those whose families were concerned about the possibility of lead exposure, for example due to living in older housing or near to an industrial site, or due to the presence of symptoms in the child. Analyses suggested that living in older housing (probably containing lead paint) was associated with raised BLLs, and the authors report than most of the homes in Evansville were built before 1978. The authors also note that Evansville has widespread soil contamination with lead due to industrial activity. Their analyses did not identify a significant link between the levels of lead in soil at the child's house and their BLL, but this analysis only included 81 children so may not be powered to detect a difference. Not all cases of elevated BLL were confirmed, so the prevalence figures may also not be entirely accurate. The prevalence of raised BLLs (above 5 µg/dL but below 10 µg/dL) appears very high compared to other studies. The soil contamination and high level of older housing suggest that these findings may not be applicable to less industrial areas with newer housing.

Appendix number	3
Relevant criteria	1
Publication details	Kennedy BS, Doniger AS, Painting S, Houston L, Slaunwhite M, Mirabella F, et al. Declines in elevated blood lead levels among children, 1997-2011. American Journal of Preventive Medicine. 2014;46(3):259-64.
Study details	Time trend study, USA. Data from the CDC's laboratory surveillance were used to look at trends from 1997 to 2011 for the US as a whole and for New York State (excluding New York City). Data for Monroe County (a county in New York State) for the same period was obtained directly from the local health department.
Study objectives	To assess temporal trends in childhood elevated BLL rates.
Inclusions	Children aged under 6 years. A confirmed elevated BLL was defined as a child with one venous blood specimen ≥10 µg/dL or any combination of 2 capillary and/or unknown blood specimens ≥10 µg/dL drawn within 12 weeks of each other. For children with a confirmed elevated blood lead in a previous year, any subsequent elevated BLL was considered confirmed, regardless of method of testing.
Exclusions	NR
Population	The number of children receiving testing and their characteristics were not reported. (Demographic information is not linked with the surveillance data). For any given year each child was counted only once (for example even if they had more than one test).
Results/outcomes	Prevalence of BLL ≥10 µg/dL in children decreased from 13.4% to 1.1% in Monroe County, 6.3% to 1.0% in New York State and 7.6% to 0.6% in the USA between 1997 and 2011. Prevalence of BLL ≥5 µg/dL was only given for Monroe County, and was displayed graphically. It peaked at 40% in 1995, and decreased after this to about 5% in 2012. The rate of decline was significantly faster in Monroe County than New York State, 2.4-fold faster than that in New York State and 1.8-fold faster than that in the USA as a whole ($p<0.001$). The childhood blood lead testing rate was reported to be higher in Monroe County than in New York State and the US; however, testing increased for all 3 areas.
Comments	This study did not provide data on the rate of BLLs ≥ 5 µg/dL in the US as a whole

	(potentially because this was prior to the CDC lowered the threshold for triggering public health intervention to this lower level). The study gives population estimates for Monroe County, New York State and the US as a whole but does not report the recruitment process or participation rate for this study. It is unclear whether it gives national or regional representation of all children aged 1-5 years. Universal BLL screening was said to have been recommended by the CDC in 1991. The authors state the New York State mandated blood lead testing in 1992, but in 1994 they report the rate of testing in Monroe County was only 30%. In 2012 it was about 25% (displayed graphically). Overall rates of testing in the US for each year were not reported, but were reported to be lower than those for Monroe County. Therefore the prevalence rates identified may not be representative of the general population, particularly if those tested are self-selecting or being targeted due to high risk.

Appendix number	4
Relevant criteria	1
Publication details	McClure LF, Niles JK, Kaufman HW. Blood Lead Levels in Young Children: US, 2009-2015. Journal of Pediatrics. 2016;175:173-81.
Study details	Retrospective time trend study USA (50 states and the District of Columbia)
Study objectives	To evaluate trends in BLLs in children <6 years of age, and to expand on the National Health and Nutrition Examination Survey (NHANES) data with a much larger national group and additional detail.
Inclusions	Data was included on children <6 years of age, corresponding to the CDC age definition for high risk.
Exclusions	BLL results without gender information were excluded from gender analysis.
Population	n=5,266,408 BLL results overall in children <6 years, but the focus of the analyses was the 3,803,070 BLLs measured from venous blood samples. The testing performed from May 2009 through April 2015 (3 years before and after the 2012 CDC change from the 10 mg/dL "level of concern" to the 5.0 mg/dL reference interval threshold). Results were from the Quest Diagnostics national clinical laboratory database. To avoid duplication, when 2 or more tests were associated with the same individual, only the first venous result (or the first capillary result if there were no venous results) was included.
Results/outcomes	Elevated BLLs were found in 2.95% of children (≥5.0 mg/dL). 2009-10: 3.67%, 2014-15: 2.59% Elevated BLLs were found in 0.58% of children (>10 µg/dL). 2009-10: 0.74%, 2014-15: 0.55% The factors associated with increased risk of BLLs (≥5.0 mg/dL) were: • male gender: adjusted OR 1.11, 95% CI 1.09 to 1.13 • living in an area in the top poverty quintile: aOR 1.64, 95% CI 1.61 to 1.67 • living in an area with the highest quintile of pre-1950s housing: aOR 2.50, 95% CI 2.46 to 2.54 • living in certain geographical regions (Health and Human Services regions 1, 3, and 7): aOR 2.23, 95% CI 2.20 to 2.26)

	Factors associated with reduced risk were being a private payer for healthcare (aOR 0.84, 95% CI 0.82 to 0.85), later study year of sample (aOR 0.92, 95% CI 0.91 to 0.92), or living in an area in the top wealth quintile (aOR 0.65, 95% CI 0.64 to 0.67). BLLs declined over time for most groups analysed.
Comments	The population tested is not necessarily representative of the general population. The authors note that it is possible that some there was some selection bias towards those at higher risk, but as their 97.5th percentile measurement was similar to that from another study which used representative sampling methods (the NHANES study) they felt this bias was likely to be minimal. However, this appeared to refer to an older NHANES report (covering 2007 to 2010). A more recent NHANES survey data (reported below in the study by Tsoi et al.)[15] estimated that only 0.5% of children aged 1 to 5 in the US had BLLs ≥5µg/dL in 2013-2014, much lower than the 2.95% reported for 2014-2015 in this study. This supports that selection bias may be occurring. This needs to be weighed up against the much larger sample in the current study (3.8 million children). The authors of the study were Quest Diagnostics employees and the data was from their laboratories but the company was reported to have no other role in the preparation of the study.

<table>
<tr><td>Appendix number</td><td>5</td></tr>
<tr><td>Relevant criteria</td><td>1</td></tr>
<tr><td>Publication details</td><td>Tsoi MF, Cheung CL, Cheung TT, Cheung BM. Continual Decrease in Blood Lead Level in Americans: United States National Health Nutrition and Examination Survey 1999-2014. Am J Med. 2016 Nov;129(11):1213-1218.</td></tr>
<tr><td>Study details</td><td>The study analysed data collected as part of the National Health Nutrition and Examination Survey (NHANES) 1999-2014

Venous blood samples were collected and blood lead levels measured in centralised laboratory using a standard protocol. The limits of detection were 0.3 mg/dL in 1999-2002, 0.28 mg/dL in 2003-2004, 0.25 mg/dL in 2003-2012, and 0.07 mg/ dL in 2013-2014. Blood lead levels below the lower limit of detection were given a value equal to the lower detection limit divided by the square root of 2.

Elevated blood lead levels were defined as ≥5 mg/dL.</td></tr>
<tr><td>Study objectives</td><td>To assess the trend in blood lead levels in the USA between 1999 and 2014.</td></tr>
<tr><td>Inclusions</td><td>The NHANES survey sample is selected to be nationally representative. Each participant represents about 50,000 noninstitutionalised US citizens. The current study analysed data for participants who had blood lead levels measured. The study did not report what proportion of the overall sample this was and whether this had any impact on the representativeness of the sample.</td></tr>
<tr><td>Exclusions</td><td>Individuals with no blood lead results available.</td></tr>
<tr><td>Population</td><td>6,684 children (3,473 boys, 3,211 girls) aged 1-5 years old. (Entire sample assessed in the study was 63,890 individuals including children and adults). Participant characteristics were not reported separately for the 1-5 year old age group. Different participants were surveyed in each survey year (i.e. the same participants were not followed over the entire study period).</td></tr>
<tr><td>Results/outcomes</td><td>The proportion of children aged 1-5 years with blood lead levels ≥5µg/dL decreased from 9.9% (95% CI, 7.5-12.9) in 1999-2000 to 0.5% (95% CI, 0.3-1.0) in 2013-2014 (p <0.001).

Mean blood lead levels (µg/dL) decreased significantly in boys and girls aged 1 to 5 between 1999 and 2014 (p<0.001 for both genders):
<table>
<tr><th>Years</th><th>Boys
µg/dL (95% CI)</th><th>Girls
µg/dL (95% CI)</th></tr>
<tr><td>1999-2000</td><td>2.14 (1.97-2.32)</td><td>2.37 (2.16-2.61)</td></tr>
<tr><td>2001-2002</td><td>1.77 (1.64-1.91)</td><td>1.64 (1.53-1.76)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>2003-2004</td><td>1.76 (1.65-1.88)</td><td>1.78 (1.64-1.92)</td></tr>
<tr><td>2005-2006</td><td>1.47 (1.38-1.57)</td><td>1.45 (1.37-1.55)</td></tr>
<tr><td>2007-2008</td><td>1.54 (1.44-1.25)</td><td>1.49 (1.38-1.60)</td></tr>
<tr><td>2009-2010</td><td>1.36 (1.31-1.41)</td><td>1.17 (1.10-1.24)</td></tr>
<tr><td>2011-2012</td><td>1.18 (1.13-1.23)</td><td>0.91 (0.84-0.99)</td></tr>
<tr><td>2013-2014</td><td>0.81 (0.77-0.86)</td><td>0.75 (0.71-0.80)</td></tr>
</table>
The estimated 97.5th percentile of the blood lead level in children aged 1-5 years in NHANES 2011-2014 was 3.48 µg/dL.
</td></tr>
<tr><td>Comments</td><td>The survey aims to be nationally representative, and has well documented methods.

Lead exposure is likely to vary geographically with proximity to industrial sites producing lead. The relatively small number of children assessed (about 800 per year) may not fully capture this geographical variability.</td></tr>
</table>

Appendix number	6
Relevant criteria	4
Publication details	Ossiander EM. A systematic review of screening questionnaires for childhood lead poisoning. Journal of public health management and practice. 2013;19(1):E21-9.
Study details	Systematic review. Searches were carried out in MEDLINE/PubMed in 2005 and then again in 2009. Reference lists of relevant studies were hand searched, and additional database searches carried out for other studies by authors of relevant studies. Results of the studies were pooled using random effects meta-analysis. To assess screening test accuracy, the authors summarised sensitivity and specificity; a figure of 1 was considered to indicate a performance only as good as chance, with a figure of 2 indicating perfect performance.
Study objectives	To evaluate the ability of lead screening questionnaires to predict lead poisoning risk among children (ie, BLLs ≥10 µg/dL)
Inclusions	Articles reporting the evaluation of a predesigned questionnaire that was implemented in the manner that a lead risk screening questionnaire would be used.
Exclusions	Studies in which answers to the risk screening questions were obtained from parents after they were given the results of their child's blood lead test. Studies which designed and evaluated a questionnaire using the same sample. Assessments of individual questions.
Population	Age of children not specified
Intervention/test	Screening questionnaires
Comparator	Blood lead test (details not specified)
Results/outcomes	20 articles met inclusion criteria: including 28 separate questionnaire evaluations for BLL >10 µg/dL. Most studies assessed the Centers for Disease Control and Prevention's (CDC's) 1991 5-item questionnaire; none assessed the CDC's 1997 questionnaire. **CDC 1991 questionnaire (17 studies)** **Sensitivity** ranged from 0.25 to 0.87 Pooled mean estimate 0.61 (95% CI 0.53 to 0.68) **Specificity** from 0.31 to 0.80 Pooled mean estimate 0.52 (95% CI 0.45 to 0.60)

	Accuracy (sum of sensitivity and specificity) from 0.74 to 1.39 Pooled mean estimates accuracy 1.12 (95% CI 1.06 to 1.18) **<u>All other questionnaires (11 studies)</u>** **Sensitivity** ranged from 0.43 to 0.90 Pooled mean estimate 0.76 (95% CI 0.68 to 0.85) **Specificity** ranged from 0.17 to 0.66 Pooled mean estimate 0.41 (95% CI 0.33 to 0.49) **Accuracy** ranged from 0.94 to 1.27 Pooled mean estimate reported in the main text as 1.13 (95% CI 1.06 to 1.20) [reported in the abstract as 1.12 (95% CI 1.06 to 1.18)]
Comments	This systematic review provides a clear description of their methods, inclusion and exclusion criteria. However, there were some limitations. The full search strategy was not provided, with only a few example search terms given, and only one database searched, which reduces confidence that all relevant studies were identified. The study had only one author and there is no indication that other researchers were involved in the review process (eg, study selection). Quality of the included studies was not reported. The author noted that many of the articles did not report on sensitivity or specificity, and those that did rarely provided confidence intervals, or assessed the predictive ability of the questionnaire compared to chance.

Appendix number	7
Relevant criteria	4
Publication details	Etchevers A, Glorennec P, Le Strat Y, et al. Screening for elevated blood lead levels in children: Assessment of criteria and a proposal for new ones in France. International Journal of Environmental Research and Public Health. 2015;12(12):15366-78.
Study details	Cross-sectional survey 2008-9, France. Recruitment was by 143 hospital paediatrics departments in mainland France and French regions overseas (French West Indies and Reunion Island). Hospitals were stratified by region and risk of lead poisoning according to factors such as prevalence of old and substandard housing and industrial pollution. Hospitals in high-risk regions were said to be intentionally oversampled. Sample weighting by region, gender, age and eligibility for health insurance was then used to generate precise estimates that would represent all young children in France.

Study objectives	To evaluate the performance of the current screening questionnaire in identifying children with BLLs higher than 5 µg/dL in France, and to propose new criteria to better detect children over this threshold.
Inclusions	Children aged between 6 months and 6 years.
Exclusions	Children were excluded from the main analysis if a parent replied "don't know" to any question in the screening survey. An analysis was also carried out to look at the effect of considering this response as if it were a "yes".
Population	n=3,831 children already having venous blood sampling in hospital for medical reasons.
Intervention/test	A questionnaire collecting socioeconomic, behavioural and environmental factors was administered by paediatricians and nurses at the hospitals, along with a blood test. Answers were collected from parents before they received the results of the blood lead test. If children were identified as having one or more risk factors through the questionnaire they were considered screen positive (these children would be offered a blood lead test in the national screening programme). The screening questionnaire includes 8 self-reported criteria relating to exposure to pre-1949 housing with peeling or chipping paint or renovation or remodelling, tendency to scrape off or nibble paint, exposure to lead water risk or areas near industrial lead source, living with individuals with lead poisoning or an adult with a job or hobby involving exposure to lead, or having recently moved to France. In the current study information was not available on parental hobbies or potential exposure to lead from industrial sources. The study calculated the performance of the current screening criteria for detecting BLLs ≥5 µg/dL. It also used logistic regression to look at ability of existing or alternative screening criteria to predict BLLs above the 97.5th percentile threshold (4.4 µg/dL; too few children were above the 5 µg/dL threshold to use this level in this analysis).
Comparator	Venous blood test of BLLs.
Results/outcomes	• 23.6% of the children met at least one positive screening criterion • 44.0% had no positive criterion • 32.4% of the parents replied "don't know" to at least one question on the screening questionnaire The most prevalent criteria in children with BLL ≥5 µg/dL were: • parents occupationally exposed to lead • living in pre-1949 housing with renovation work The sensitivity of the questionnaire for detecting BLLs ≥5 µg/dL where parents reported at least one positive criterion in the screening questionnaire was 0.51 (95% CI 0.26 to 0.75) and specificity was 0.66 (95% CI 0.62 to 0.70).

TP	FP	FN	TN	Total with data	Missing Data

23	831	17	1402	2,273 (59%)	1,558 (41%)

Abbreviations: TP: true positive; FP: false positive; FN: false negative; TN: true negative

Precision of the sensitivity figure was low due to a small number of children having BLLs ≥5 µg/dL (67 children) and the high rate of missing data or "don't know" responses in the sample.

The "don't know" responses mainly concerned housing age and lead water pipes. Sensitivity was improved (0.65, 95% CI 0.47 to 0.82) by considering "don't know" responses as positive, but this also reduced specificity to 0.44 (95% CI 0.40 to 0.48).

The authors interpreted these results as showing that risk factors assessed in the screening questionnaire need to be refined to detect the lower threshold of lead exposure now required (5 µg/dL).

On the basis of their logistic regression analysis they generated 9 new screening criteria, including gender (female), drinking tap water when lead pipes are present, recent arrival in France, mother born outside of France, parent smoking in the house >5 hours a day, living in pre-1949 housing with paint peeling, parental occupational exposure to lead, high house occupancy (≥3 per room), and proportion of substandard pre-1949 housing in the region. These criteria improved the area under the curve to 0.86 (95% CI 0.80 to 0.91) from 0.76 (95% CI 0.69 to 0.84) for the existing screening criteria, for predicting BLLs ≥4.4 µg/dL. The maximal sensitivity obtained with the new criteria was 0.96 and specificity of 0.55, according to the ROC curve. However, the inclusion of gender was thought to be an artefact due to sample weighting so it was not recommended for routine inclusion in the screening criteria.

Comments

This study was also reported by Etchevers et al 2014 (reported above in Appendix 1 and under Criterion 1).

Only 67 children had BLLs higher than ≥5 µg/dL, so estimates of test performance were not well powered.

Not all questions from the existing French screening questionnaire were included in the study, so results may not be representative of its true performance.

Children may not be nationally representative.

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of	N	Unclear	Children were recruited from 143 hospital paediatric departments

	population enrolled?			in France or French regions overseas. The authors report that previous studies have shown that using geographical indicators have helped detect children at higher risk. Post-stratification weighting was used which should make the sample nationally representative.
	Case-control design avoided?	Y	Low	Not a case control
	Inappropriate exclusions avoided?	N	High	Children were excluded if a parent had answered "don't know" to any questions, however there may have been positive responses to other questions. However, they did also analyse results for all of these individuals as though they were screen positives to determine whether there was an effect, and this increased sensitivity slightly (to 65%) but reduced specificity (to 44%).
	Domain II: Index Test			
	Index test results interpreted without knowledge of reference standard results?	Y	Low	Answers were collected from parents before receiving the results of the blood tests.
	Threshold pre-specified?	Y	Low	A threshold of ≥50 µg/L was specified in the report
	Domain II: Reference standard			
	Reference standard likely to correctly classify condition?	Y	Low	Method for blood sampling unclear in this publication. However this same sample is described in another paper by the same authors and this clarifies that venous blood samples were used
	Reference standard results interpreted	Unclear	Unclear	Not reported in the paper

	without knowledge of index test results?			
	Domain IV: Test strategy flow and timing			
	Appropriate interval between index test and reference standard?	Unclear	Unclear	Not reported in the paper
	Did all participants receive same reference standard?	Y	Low	
	All patients included in analysis?	N	High	Large number of children with missing data (see table in results above)
	Applicability			
	Applicable to UK screening population of interest?	Y	Low	Unclear whether prevalence differs from the UK, but France seems likely to be similar
	Applicable to UK screening test of interest?	Y	Low	No specific screening test has been suggested as the test of interest, however, a non-invasive test such as this is likely to be of the greatest interest.
	Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	BLL of ≥5 µg/dL.

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