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Screening for Elevated Blood Lead Levels in Children: A Systematic Review for the U.S. Preventive Services Task Force

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5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
Pacific Northwest Evidence-based Practice Center
Oregon Health & Science University
Mail Code: BICC
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Amy G. Cantor, MD, MPH
Rob Hendrickson, MD
Ian Blazina, MPH
Jessica Griffin, MS
Sara Grusing, BA
Marian S. McDonagh, PharmD

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Structured Abstract

Background: In 2006, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine screening for elevated blood lead levels in asymptomatic children ages 1 to 5 years who are at increased risk for lead poisoning (I recommendation), and recommended against routine screening in those at average risk (D recommendation).

Purpose: To synthesize evidence on the effects of screening, testing, and treatment for elevated blood lead levels in children age 5 years and younger in the primary care setting, to update a prior USPSTF review on screening for elevated blood lead levels in childhood.

Data Sources: Cochrane CENTRAL and Cochrane Database of Systematic Reviews (through June 2018), and Ovid MEDLINE (1946 to June 2018), reference lists, and surveillance through December 5, 2018.

Study Selection: English-language trials and observational studies of screening effectiveness, test accuracy, and benefits and harms of screening and interventions in asymptomatic children age 5 years and younger.

Data Extraction: One investigator abstracted details about study design, patient population, setting, screening method, followup, and results. Two investigators independently applied prespecified criteria to rate study quality using methods developed by the USPSTF. Discrepancies were resolved through consensus.

Data Synthesis (Results): A total of 22 studies were included in this review (N=10,449). No studies directly evaluated clinical benefits or harms of screening versus not screening children for elevated blood lead levels. More than one positive answer on the five-item 1991 Centers for Disease Control and Prevention screening questionnaire was associated with a pooled sensitivity of 48 percent (95% confidence interval [CI], 31.4% to 65.6%) and specificity of 58 percent (95% CI, 39.9% to 74.0%) for identifying children with a venous blood level greater than 10 µg/dL (5 studies; N=2,265). Adapted versions of the questionnaire did not demonstrate improved accuracy. Capillary blood lead testing demonstrated sensitivity of 87 to 91 percent and specificity greater than 90 percent, compared with venous measurement (4 studies; N=1,431). Counseling and nutritional interventions or residential lead hazard control techniques did not reduce blood lead concentrations in asymptomatic children, but studies were few and had methodological limitations (7 studies; N=1,419). A trial of dimercaptosuccinic acid chelation therapy found reduced blood lead levels in children at 1 week to 1 year but not at 4.5 to 6 years (N=780), while another trial found no effect at 1 and 6 months (N=39). Seven-year followup assessments showed no effect on neuropsychological development; a small deficit in linear growth (height difference at 7 years in treated patients, 1.17 cm [95% CI, 0.41 to 1.93 cm]) and poorer cognitive outcomes reported as the Attention and Executive Functions subscore of the Developmental Neuropsychological Assessment (unadjusted difference, -1.8 [95% CI, -4.5 to 1.0]; adjusted *P*=0.045) in children treated with dimercaptosuccinic acid chelation.

Limitations: Limited to English-language articles; quality and applicability of studies were limited due to study design, poor reporting of statistical outcomes, and loss to followup. Studies were lacking on the effectiveness of screening or treatments in reducing elevated blood lead levels or improving health outcomes in children. There was no direct evidence on the harms of screening children for elevated blood lead levels.

Conclusions: Evidence on the benefits and harms of screening children for elevated blood lead levels is lacking. Screening questionnaires are not accurate for identifying children with elevated blood lead levels. Capillary blood testing is slightly less accurate than venous blood testing for identification of elevated blood lead levels. Treatment studies of chelating agents, often combined with environmental or household interventions, were not associated with sustained effects on blood lead levels but were associated with harms.

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Chapter 1. Introduction and Background

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2006 recommendation on screening for elevated blood lead levels in children. This update focuses on studies published since the prior USPSTF systematic review[1] of this topic as well as studies included in the prior review.

In 2006, the USPSTF found insufficient evidence for screening asymptomatic children ages 1 to 5 years at increased risk for elevated blood lead levels (BLLs) (I recommendation). The USPSTF recommended against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at average risk (D recommendation) based on evidence that did not support any benefits conferred with detection or early intervention among children with asymptomatic or mild/moderate lead levels. In addition, good-quality evidence from the 2006 review showed that interventions did not result in sustained decreases in BLLs, and chelation treatment specifically was associated with a slight diminution in cognitive performance.

Condition Background

Condition Definition

Elevated BLL is defined as greater than 5 µg/dL, according to the Centers for Disease Control and Prevention (CDC).[2] Although no safe level of lead exposure exists, this is the level at which further clinical monitoring or treatment is recommended for children.[2] Previously, children with a BLL of 10 µg/dL or greater were identified as having a blood lead "level of concern," and the CDC recommended that identification of children with a BLL of 10 µg/dL or greater should prompt public health action and followup testing by state or local health departments.[3] However, in 2012, the CDC's Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP) lowered the level, because no safe level of lead exposure has been established, and it determined that a threshold of 10 µg/dL or greater likely misses children at risk of adverse health effects.[4] The ACCLPP recommended using a reference range value based on the estimated 97.5 percentile of the BLL distribution among children ages 1 to 5 years calculated from two 2-year cycles of National Health and Nutritional Examination Survey (NHANES) data.[4] In 2010, the upper value of the reference range was 5 µg/dL.[2] The ACCLPP also recommended that clinicians monitor children with BLLs between 5 and 10 µg/dL based on evidence that higher BLLs are associated with IQ deficits, attention-related behaviors, and poor academic achievement.[4] Current reference ranges are based on population levels from NHANES BLL distribution; these do not define safe lead levels but are the level at which further clinical monitoring and treatment is recommended. The reference range may continue to change with population prevalence.

Prevalence and Burden of Disease/Illness

Lead causes a number of adverse health effects primarily affecting the central nervous, hematopoietic, hepatic, and renal systems.[5] Manifestations are variable, but there is a general correlation between higher BLLs and the presence of symptoms. Acute toxicity resulting from intense lead exposure over a short duration is very uncommon and primarily associated with occupational exposure or ingestion of lead-containing products in children.[5] Clinical symptoms of acute lead exposure include muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma.[5]

Many health effects associated with chronic exposure to elevated BLLs are irreversible. Compared with other organ systems, the nervous system is the most sensitive and chief target for lead-induced toxicity.[5] The severity of lead toxicity is correlated with higher BLLs and may include delirium, lack of coordination, convulsions, paralysis, coma, ataxia, and death. Lead exposure can lead to anemia by directly affecting the synthesis of hemoglobin (by inhibiting various key enzymes involved in the heme synthesis pathway) and by reducing the life span of circulating erythrocytes by increasing the fragility of cell membranes.[6]

Adverse effects in children include behavioral and learning problems, lower IQ and hyperactivity, impaired growth, hearing problems, and anemia.[7] Young children absorb lead at a higher rate (40% to 50% of ingested lead) compared to adults (3% to 10%) and are especially vulnerable to the neurological effects of lead.[8] The developing nervous system is thought to absorb a higher fraction of blood lead compared with adults.[9] New findings also suggest lead exposure in children can result in a range of cardiovascular, immunological, and endocrine adverse health effects.[4] Few studies of the long-term consequences of childhood lead poisoning exist. However, in a 50-year followup of 35 adult survivors of childhood lead poisoning, all of whom had been symptomatic, cognitive dysfunction,[10] hypertension,[11] and offspring with learning disabilities[12] were more prevalent than in matched adult controls.

Public health efforts to reduce exposure to lead in the United States (e.g., removal of lead from household paints and gasoline) are considered major successes. Although it is difficult to measure changes in morbidity attributable to lead exposure, the percentages of children and adults with elevated BLLs have declined significantly over the past few decades.

Data from the 1976 to 1980 cycle of NHANES estimated that 88 percent of children ages 1 to 5 years had BLLs of 10 µg/dL or greater. This percentage fell sharply in the following decades to 4.4 percent from 1991 to 1994, then 1.6 percent during the 1999 to 2002 cycle, and was estimated to be 0.8 percent in the most recent 2007 to 2010 survey cycle.[2] NHANES data from 2007 to 2010 estimated that 3.1 percent of children ages 1 to 2 years had BLLs of 5 µg/dL or greater.[4] Estimates varied by race/ethnicity, socioeconomic status, and age of housing. Among children ages 1 to 2 years, 7.7 percent of non-Hispanic black children had BLLs of 5 µg/dL or greater, compared with 3.2 percent of non-Hispanic white children and 1.6 percent of Mexican American children; 3.1 percent of males and 3.2 percent of females had BLLs of 5 µg/dL or greater in the same survey.[13] Differences were also observed based on socioeconomic status; 6.0 percent of children living in a household with a poverty-to-income ratio of less than 1.3 had BLLs of 5 µg/dL or greater, compared with 0.5 percent of children living in a household with a

poverty-to-income ratio of 1.3 or greater (ratio <1.00 indicates an income below the official definition of poverty). During the NHANES 1999 to 2002 cycle, children living in pre-1950 housing were 10 times more likely to have BLLs of 5 µg/dL or greater than children living in homes built after 1978. By the 2007 to 2010 cycle, children living in pre-1950 housing were 4 times more likely to have BLLs of 5 µg/dL or greater than children living in homes built after 1978.[13]

Etiology and Natural History

Lead is a heavy metal that occurs naturally in the environment. Unique properties of lead (e.g., high malleability, low melting point, and resistance to corrosion) resulted in its widespread use in various industries. Lead has become widely distributed and mobilized in the environment resulting in increasing human exposure and uptake over time.[14]

Common sources of lead exposure include the following: lead-based paint, contaminated soil (e.g., by exterior lead-based paint, historical lead emitting industrial sites, or gasoline), lead-contaminated water (e.g., by lead plumbing), and dust contamination by chipping or chalking of lead-based paint and tracked-in soil.[14] In the United States, leaded gasoline began to be phased out in 1973 and was banned by 1996. From 1980 to 2010, exposure to lead fumes from leaded gasoline decreased by 89 percent.[15] Lead-based paints were banned for use in housing in 1978. All houses built before 1978 are likely to contain some lead-based paint and the deterioration of this paint is an important source of lead in older homes.[14] Although lead was restricted in plumbing material in 1986, older homes and neighborhoods may still contain lead service lines, lead connections, or other lead-based plumbing materials.[16] The release of lead from lead-based plumbing materials into drinking water is variable and influenced by factors such as water softness, temperature, acidity, and corrosion control techniques.[17] Flint, Michigan provides an example of increased lead contamination of drinking water related to changes in water sources and treatment, including the use of disinfectants.[18]

Children are exposed to lead in a variety of ways. Since the removal of lead from gasoline, lead-based paint has become the major source of lead exposure for children in the United States.[19] Other important pediatric sources of lead exposure include elevated maternal blood lead concentration during pregnancy and breastfeeding; exposure to lead-contaminated soil, food, or water; and lead in toys.[3] Young children frequently place objects in their mouths resulting in ingestion of lead-contaminated dust and soil. Children and infants may be exposed to lead via drinking water or reconstituted formula,[20] placental transfer of lead during pregnancy to the fetus, or maternal transfer of lead to infants through breast milk.[21] Children can be exposed to lead via take-home exposures by adults who work with lead.[19] Parental take-home exposures from work or hobbies can be easily transferred to children through lead dust found on hair, clothes, or tools. Compared with adults, children have a higher rate of physiological uptake of lead.

Once exposed, nutritional factors are known to affect lead absorption and toxicity. Iron-deficient or calcium-deficient diets may lead to more efficient lead absorption.[22] Following absorption, lead is distributed to the blood, soft tissues, and bone. In blood, 99 percent of lead is bound to erythrocytes and the remaining 1 percent is free in the plasma to exchange with soft tissues

(kidney, brain, liver, and bone marrow). More than 90 percent of lead in the body is stored in bone.[23]

Risk Factors

Risk factors for lead exposure include: socioeconomic disadvantage; living in an area with lead industry; renovation or deterioration of older lead-painted houses; and previously living in developing countries where leaded gasoline is still used.[14] Among children, socioeconomic factors such as lower family income, older age of housing, and poorer nutritional status predict exposure to lead.[4,13]

Rationale for Screening/Screening Strategies

Current clinical guidelines and policies emphasize primary prevention of lead exposure. The rationale for screening in primary care settings is to identify children for whom primary prevention was unsuccessful, so that interventions can be initiated to reduce lead levels and minimize or prevent the neurodevelopmental adverse effects of lead poisoning.

As the prevalence of elevated BLLs has declined, clinical practice has shifted from universal to targeted screening that incorporates education about primary prevention.[24] Several questionnaires have been developed to identify children at higher risk of elevated BLLs. The mostly widely used is the CDC questionnaire, developed in 1991, which consists of five questions about living in or visiting a house built before 1960 with chipping paint or undergoing renovation; having a sibling or close contact being followed or treated for lead poisoning (BLL ≥15 µg/dL); living with an adult who is exposed to lead through work or hobbies; and living near lead-based industry. The CDC has recommended the use of the questionnaire, with a positive or "don't know" answer to any of the five questions indicating the need for a blood lead test.[25] However, given more recent recognition of the limitations of this questionnaire, the CDC recommends that public and clinical health professionals collaborate to develop screening plans that are responsive to local conditions by using local data.[25]

Screening options to detect an elevated BLL include 1) directly measuring the BLL through venous or capillary blood sampling or 2) measuring the effect of lead exposure on hemoglobin synthesis using either a free erythrocyte or zinc protoporphyrin (EP) assay (via venous blood sampling).[24] Measuring BLLs using capillary blood sampling is simpler than venous sampling and is the recommended initial method for lead screening.[26] However, if performed incorrectly, capillary samples may be contaminated with exogenous lead and can yield false-positive results.[27] Potential sources of contamination include inadequate use of gloves by phlebotomists, use of alcohol wipes contaminated with lead-based ink, inadequate cleansing of the child's finger, and failure to wipe off the first drop of blood.[24] Patients who have elevated BLLs on capillary samples must have confirmatory venous blood testing.[28] EP levels usually are not elevated until BLLs are greater than 30 µg/dL. Therefore, EP levels are not an accurate assessment of lower levels of lead toxicity and are not recommended for screening.[24] In addition, EP levels are elevated in other conditions, including iron deficiency and inherited porphyrias.[24]

Interventions/Treatment

The management of elevated BLLs in children varies depending on the confirmed BLL and other factors. Identifying the source of lead exposure is a key to preventing ongoing or repeated exposure and remains the mainstay of treatment for lead exposure.

Educational and Environmental Interventions

Educational interventions address parental awareness of lead exposure pathways, hygiene, and household dust control measures to prevent ingestion of dust and soil. Environmental (household) interventions include specialized cleaning, repairs, maintenance, soil abatement (e.g., removal and replacement), painting, and temporary containment of lead hazards.

Nutritional Interventions

The role of nutritional supplementation in reducing blood lead concentration among children with elevated BLLs is unclear. Calcium, dietary iron, and other supplements are thought to decrease the intestinal absorption of lead. This is supported by epidemiologic studies that have demonstrated an increased prevalence of iron deficiency among children with lead poisoning.[29,30] However, the association is inconsistent, and evidence of an association between iron intake and lead levels in iron-replete children is lacking.

Chelation Therapy

In children, chelation therapy is recommended for severe lead toxicity (defined by a venous BLL of ≥70 µg/dL or having symptoms of encephalopathy) and moderate toxicity (symptomatic or BLL between 45 and 69 µg/dL) and is generally reserved for symptomatic individuals. Chelating agents work as binding agents that remove metals (i.e., lead) from the blood and soft tissues, including the brain, to reverse acute encephalopathy and alleviate vomiting, abdominal pain, anemia, and renal insufficiency caused by lead toxicity. Dimercaprol (dimercaptosuccinic acid [DMSA] or succimer) is a commonly used agent for the oral chelation of lead in children with levels at or above 45 µg/dL,[31] and d-penicillamine is rarely used in patients who do not tolerate DMSA. In regions where cost is an issue, d-penicillamine may be used, but it is not recommended as a first-line agent. However, multiple potential harms of chelation therapy have been described, including side effects such as rash, neutropenia, elevation of serum liver transaminases, and gastrointestinal upset, in addition to acute side effects such as injection site pain, nausea, vomiting, headache, paresthesias, and tremor.[32] Serious adverse reactions may include hypertension, tachycardia, infection site abscess, and fever.[28]

Current Clinical Practice/Recommendations of Other Groups

Current Clinical Practice

Data are lacking on the current proportion of primary providers who screen asymptomatic children for elevated BLLs. A 1996 survey (N=734) of pediatricians, members of the American Academy of Pediatrics (AAP), found that 53 percent reported screening all patients ages 9 to 36

months, 39 percent reported screening some patients, and 8 percent reported screening none of their patients. Among physicians who reported screening for elevated BLLs, 96 percent used a BLL assay and 3 percent used a porphyrin assay. Of those who used a BLL assay, 39 percent collected blood for screening using a finger stick method and 52 percent collected blood using venipuncture (9% did not report the method used). The primary risk factors that selective screeners identified were history of pica (94%), living in an older home with recent renovations (92%), living in an older home with peeling paint (93%), and having a sibling who had an elevated BLL (88%).[33]

When a child with an elevated BLL is identified, confirmatory and repeat testing is recommended, followed by management based on lead levels and symptoms. Important management strategies for asymptomatic children with BLLs of 45 µg/dL or less include removing the source of lead exposure, testing close contacts and other children in the household at risk, and lead abatement and education. For children who are symptomatic or with higher blood lead concentration (≥45 µg/dL), in addition to the management strategies mentioned above, emergent consultation with an expert is recommended for consideration of hospitalization, stabilization, and chelation therapy based on the degree of symptoms. Specific guidelines exist for followup depending on the degree of elevation of BLL.[25]

Recommendations of Other Groups

Table 1 summarizes current screening recommendations from other organizations. Contrary to the 2006 USPSTF recommendation, existing recommendations from the AAP, CDC, and American College of Preventive Medicine all state that children at high risk for lead exposure should receive screening.[4,23,34-36] The American College of Preventive Medicine defines high-risk groups as those receiving Medicaid or WIC, living in a community with 12 percent or greater prevalence of BLLs at 10 µg/dL or greater, living in a community with 27 percent or greater of homes built before 1950, or meeting one or more high-risk criteria of a lead screening questionnaire. Questionnaires tailored to specific communities may include questions about the use of home remedies and cosmetics, country of origin, and behavioral risk factors.[34] Bright Futures recommends screening in accordance with state law, and universal screening at ages 12 and 24 months in states with no screening program in place.[35] In 2016, AAP recommended screening according to federal, state, and local requirements, with targeted screening of populations including immigrant, refugee, and internationally adopted children when they arrive in the United States; children ages 12 to 24 months living in communities with 25 percent or greater of housing built before 1960 or a 5 percent or greater prevalence of BLLs of 5 µg/dL or greater; and children with identified lead hazards or a home built before 1960 that is in poor repair or renovated in the past 6 months.[37]

Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol in accordance with USPSTF procedures.[38] The scope and Key Questions for this report were developed by Evidence-based Practice Center investigators in collaboration with the USPSTF and the Agency for Healthcare Research and Quality, and informed by evidence gaps identified from the prior review.[1] In addition, three Contextual Questions were requested by the USPSTF. Contextual Questions address topics important to the USPSTF recommendations, but are reviewed by summarizing evidence from key informative studies rather than by using systematic review methodology. Key Questions and Contextual Questions are listed below. Investigators created an analytic framework incorporating the Key Questions and outlining the patient populations, interventions, outcomes, and potential adverse effects, as well as the direct and indirect pathways from screening to health outcomes (**Figure 1**). A research plan was externally reviewed and modified prior to finalization.

Key Questions

1. Is there direct evidence that screening for elevated BLLs in asymptomatic children age 5 years and younger improves health outcomes (i.e., reduced cognitive or behavioral problems or learning disorders)?

2a. What is the accuracy of questionnaires or clinical prediction tools that identify children who have elevated BLLs?

2b. What is the accuracy of capillary blood lead testing in children?

3. What are the harms of screening for elevated BLLs (with or without screening questionnaires) in children?
4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs in asymptomatic children with elevated BLLs?
5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated BLLs?
6. What are the harms of interventions in asymptomatic children with elevated BLLs?

Contextual Questions

1. What is the reliability of capillary and venous BLL testing at various lead levels in children?
2. What is the association between reduced BLLs and improved health outcomes in asymptomatic children with elevated BLLs?
3. Are there valid risk prediction tools available that identify communities at highest risk for lead exposure that could be used in primary care practices to target screening efforts in children?

Key Question 1 focused on direct evidence of the effectiveness of screening asymptomatic children age 5 years and younger for elevated BLLs for improving future health outcomes (e.g., reduced cognitive problems, reduced behavioral problems, and reduced learning disorders)

compared with not screening. Screening refers to diagnostic testing of BLLs to identify children with unrecognized elevation of lead levels. Because such direct evidence may be limited, the remainder of the analytic framework (Key Questions 2 through 6) evaluates the chain of indirect evidence needed to link screening with improvement in important health outcomes. Links in the chain of indirect evidence include the accuracy of screening for identifying children with elevated BLLs, the effectiveness of interventions for treating children identified with elevated BLLs and reducing the incidence of complications, the association between improvements in intermediate outcomes and clinical health outcomes, and harms associated with screening and treatments. Implicit in the indirect chain of evidence is that, to understand benefits and harms of screening, it is necessary but not sufficient to show that children with elevated BLLs can be identified. It is also necessary to show that there are effective treatments for children identified with elevated BLLs.

A separate report addresses screening for elevated BLLs in pregnant women.

Search Strategies

Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through March 2017), Ovid MEDLINE (1946 through March 2017), all studies from prior reviews, and reference lists of included studies were searched for relevant studies. Search strategies are available in **Appendix A1**. An additional Ovid MEDLINE search (through October 2017) was conducted for the Contextual Questions after the initial search did not identify any studies meeting inclusion criteria. Searches were updated through June 2018. Ongoing surveillance was conducted through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on December 5, 2018.

Study Selection

Two reviewers independently evaluated each study to determine its inclusion eligibility based on predetermined inclusion and exclusion criteria developed for each Key Question (**Appendix A2**).

Populations of asymptomatic children age 5 years and younger were included, regardless of risk for elevated BLLs, but we accepted studies that included children older than age 5 years when the majority of the study population was age 5 years and younger. Studies of high- or low-risk populations were included for all Key Questions. Testing approaches included screening questionnaires and venous or capillary blood lead testing. Comparisons were screening versus no screening (Key Question 1); a questionnaire versus a reference standard (i.e., venous lead level) (Key Question 2a); capillary versus venous BLL testing (Key Question 2b); and treatment versus no treatment, placebo, or inactive control (Key Questions 3 through 5). Intermediate outcomes (e.g., BLLs) were included, as well as clinical outcomes using validated measures of cognitive or neurobehavioral outcomes in children. Other outcomes were measures of diagnostic accuracy (Key Question 2) and harms of testing (e.g., anxiety, distress, pain, or discomfort related to

testing) and treatment. Inclusion was restricted to English-language articles and studies only published as abstracts were excluded. Studies of nonhuman subjects were also excluded, and studies had to report original data. Studies conducted in countries with a "very high" Human Development Index[39] (i.e., considered applicable to U.S. populations and practice) were included; studies from countries with a "high" Human Development Index were included if no other studies were available. Included studies for Key Questions 4 through 6 (treatment of elevated BLLs) were studies of asymptomatic children conducted in any country that evaluated interventions that focused on the individual or family (i.e., counseling, nutritional interventions, residential hazard control techniques, and chelation therapy). Studies on effects of policies, laws, or community-based interventions focused on the primary prevention of lead exposure were excluded. For harms, randomized, controlled trials (RCTs) of screening and treatments, controlled clinical trials on effects of therapies on health outcomes, controlled clinical trials and prospective cohort studies on harms of therapies, and studies on diagnostic accuracy of screening questionnaires or capillary sampling were included. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists included studies and **Appendix A5** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. For studies that did not report measures of diagnostic accuracy but provided the necessary data, we calculated relative risks (RRs), likelihood ratios, positive and negative predictive values, and 95 percent CIs or p-values. Two investigators independently applied criteria developed by the USPSTF[38] to rate the quality of each study as good, fair, or poor (**Appendix A6**) and resolved discrepancies by consensus.

Data Synthesis

Two independent reviewers assessed the internal validity (quality) of the body of evidence for each Key Question ("good," "fair," or "poor") using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence (**Table 2**).[38] For diagnostic accuracy of clinical questionnaires, comparable studies were pooled using a random-effects model with the 'metandi' command in Stata version 14.2 and created hierarchical summary receiver operating characteristic (ROC) plots using the 'metandiplot' function.[40,41] The "metandi" command is a meta-analysis function for diagnostic test accuracy studies in which both the index test under study and the reference test (gold standard) are dichotomous. It assumes a bivariate normal distribution for random effects as a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives within each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies. Forest plots (without a summary measure) and summary ROC plots were also created using Review Manager version 5.3.[42]

External Review

The draft report was reviewed by content experts (**Appendix A7**), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners, and has been posted for public comment; it has been revised accordingly.

Response to Public Comment

The draft report was posted for public comment on the USPSTF Web site from October 30, 2018 to December 3, 2018. Comments encompassed requests to include results from studies of primary prevention and challenges in assessing clinical effects of lead exposure, which can take several years to manifest. However, primary prevention of lead exposure is out of scope for this review, which focused on screening and interventions to identify and reduce already elevated BLLs. As noted in the Results, studies on the long-term effects of screening or treatment of elevated BLLs are lacking.

Chapter 3. Results

The search and selection of articles are summarized in the literature flow diagram. Two reviewers independently identified 3,147 unique citations and 233 full-text articles based on predefined criteria (**Appendix A2**). A total of 21 studies met inclusion criteria for this review (N=10,449). **Appendix A3** shows the results of the literature search and selection process, **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded full-text papers.

Key Question 1. Is There Direct Evidence That Screening for Elevated BLLs in Asymptomatic Children Age 5 Years and Younger Improves Health Outcomes?

As in the prior USPSTF review, no studies directly compared the effectiveness of screening versus no screening for elevated BLLs in children age 5 years and younger on health outcomes.

Key Question 2a. What Is the Accuracy of Questionnaires or Clinical Prediction Tools That Identify Children Who Have Elevated BLLs?

Summary

Nine fair-quality studies (six included in the prior USPSTF report) reported the diagnostic accuracy of questionnaires or clinical prediction tools for identifying asymptomatic children with elevated BLLs, defined as a BLL greater than 10 µg/dL.[43-51] All studies used a BLL greater than 10 µg/dL as the reference standard. Five fair-quality studies that used the threshold of one or more positive answers on the five-item 1991 CDC screening questionnaire reported a pooled sensitivity of 48 percent (95% CI, 31.4% to 65.6%) and specificity of 58 percent (95% CI, 39.9% to 74.0%) for identifying children with a venous BLL of 10 µg/dL or greater.

Four fair-quality studies that used versions of the CDC questionnaire modified for specific populations or settings did not demonstrate improved accuracy (sensitivity range, 25% to 68%; specificity range, 49% to 58%).

Evidence

The prior USPSTF review[1] found fair evidence that a validated questionnaire can correctly identify 64 to 87 percent of children at high risk in urban and suburban populations with BLLs of 10 µg/dL or greater. However, eight of the studies in the prior review did not meet criteria for this update and were excluded due to having the wrong comparison or reference standard.[52-59] The prior report also found fair evidence that a validated questionnaire had not been adequately evaluated as a screening tool to detect higher BLLs (e.g., ≥20 to 25 µg/dL) or lead exposure in

specific populations (e.g., migrant workers, rural communities). Five studies from the prior review on accuracy of screening instruments met inclusion criteria for this update.[45,47,48,50,51] Four additional studies were identified for this update.[43,44,46,49]

Nine studies reported on the diagnostic accuracy of questionnaires or clinical prediction tools for identification of children with elevated BLLs (**Appendixes B1 and C1**).[43-51,] Five studies evaluated the accuracy of the 1991 CDC questionnaire and four evaluated versions of the CDC questionnaires modified for specific populations and settings.[43-51] The CDC questionnaire is a five-question survey developed in 1991 that aims to assess residential, household, and personal risk factors for lead exposure in children. Specific items include the age of the child's housing and the condition of the paint; siblings or playmates with BLLs of 15 µg/dL or greater; parental exposure through work or hobbies; and a home in close proximity to lead industry. Sample sizes ranged from 167 to 2,978 (total N=6,873). Mean age was not reported in six studies, was reported as 9 months in one study,[43] and reported as 28 and 31 months in two other studies.[47,49] Females comprised 46 to 51 percent of participants in five studies and sex was not reported in the other five. Seven studies were conducted in urban or suburban communities and three studies were conducted in rural communities. Two of the studies identified their population as high risk[44,46] and others did not characterize study populations by risk level; however, many of the populations surveyed were from public programs such as Medicaid or public health clinics. In all studies, children were reported as asymptomatic. The prevalence of children with a BLL of 10 µg/dL or greater ranged from 2.2 percent[47] to 29 percent.[43] In study populations characterized as higher risk, the prevalence of an elevated BLL of 10 µg/dL or greater ranged from 7.7 to 22 percent.[44,46] Nine studies were rated as fair quality. One poor-quality, retrospective study was excluded from this analysis.[60] Methodologic shortcomings included unclear enrollment methods and exclusion of some patients from analysis (**Table 3**). The poor-quality study performed retrospective surveys of exposures after BLL was known.

Five fair-quality, cross-sectional studies (total N=2,265) conducted in mostly urban[43-46] and one rural U.S. community (n=368)[47] evaluated the diagnostic accuracy of the 1991 CDC questionnaire[3] for identification of children with venous BLLs of 10 µg/dL or greater. The studies used a threshold of one or more positive answers from the five-question survey to indicate a positive screen. Across studies, sensitivity ranged from 32 to 83 percent and specificity ranged from 32 to 80 percent, with a pooled sensitivity of 48 percent (95% CI, 31.4% to 65.6%) and pooled specificity of 58 percent (95% CI, 39.9% to 74.0%) (**Figure 2**).[43-47] The positive likelihood ratio was 1.15 and the negative likelihood ratio was 0.89, indicating that either a positive or negative screen had little effect on informing the likelihood of elevated BLLs.

Four diagnostic accuracy studies[48-51] evaluated a modified 1991 CDC questionnaire by changing some of the language in the CDC questions[3] or expanding the CDC questionnaire by adding additional questions to address local risk factors to adapt the questionnaire for use in specific study populations. One study conducted in a low-income, inner city population (n=2,978) found that the adapted questionnaire had low accuracy for identifying children with elevated BLLs (sensitivity, 57%; specificity, 51%).[48] Another study (n=705) conducted in a rural setting[51] used two items from the CDC questionnaire and two additional items for rural community risk factors and found limited benefit in detecting rural children at higher risk. Compared with the CDC questionnaire, there was a 12-percent increase in sensitivity for identifying children with BLLs

of 10 µg/dL or greater (75% vs. 88%) and a 5-percent increase in negative predictive values (93% vs. 98%) using the modified questionnaire. A smaller study (n=171) conducted in rural New York[50] that added six items to the CDC questionnaire found no difference compared with the standard CDC questionnaire for predicting elevated BLLs (sensitivity, 50% vs. 50%). Another study conducted in an urban population (n=754)[49] with a 3.1 percent prevalence of a BLL of 10 µg/dL or greater found that adding two items to the CDC questionnaire did not increase accuracy for detection of children with elevated BLLs.

Key Question 2b. What Is the Accuracy of Capillary Blood Lead Testing in Children?

Summary

Four fair-quality studies conducted in the urban United States[27,61-63] found that capillary blood lead testing was associated with sensitivity of 87 to 91 percent and specificity greater than 90 percent (92% to 99%) for identification of elevated BLL compared with venous sampling; two of the studies were included in the prior USPSTF review.

Evidence

The prior USPSTF report included two studies that compared the accuracy of capillary versus venous blood lead testing.[27,63] We identified four fair-quality cohort studies assessing the diagnostic accuracy of capillary testing compared with venous sampling for elevated BLLs,[27,61-63] including the two studies in the prior report (**Appendixes B2 and C1**).[27,63] All four studies were conducted in the urban United States and were published between 1994 and 1998. Sample sizes ranged from 124 to 513 participants (total N=1,431). The mean age was 3 years in one study[63] and was not reported in the other studies. Females comprised 41 to 47 percent of the sample in three studies; the fourth study did not report sex. Two studies predominately enrolled black children,[61,63] and one study evaluated a more diverse study population (38% white, 28% black, 21% Hispanic, and 6% Asian[27]); the fourth study did not report race/ethnicity.[62] Among the three studies that reported baseline BLLs, the proportion of children with a BLL of 10 µg/dL or greater ranged from 21 to 31 percent.[27,61,62] Methodologic shortcomings of the studies included unclear methods of patient enrollment and exclusion of some patients from analysis.

At a BLL cutoff of 10 µg/dL or greater in capillary sampling, three studies reported sensitivities ranging from 87 to 94 percent, and specificities ranging from 92 to 99 percent (N=1,136).[27,61,62] For a BLL cutoff of 15 µg/dL or greater, three studies reported sensitivities ranging from 36 to 83 percent and specificities from 95 to 98 percent.[27,61,62] For a BLL cutoff of 20 µg/dL or greater, three studies reported sensitivities ranging from 78 to 96 percent and specificities from 91 to 100 percent (N=918).[27,61,63]

One study evaluated different preparation methods for capillary blood sampling (N=295)[63] (alcohol wipe; alcohol wipe and silicone barrier; soap and water followed by alcohol wipe; or soap and water, alcohol wipe, and 1% nitric acid solution). Using a capillary sampling threshold

of greater than 20 µg/dL, the most commonly employed sampling method (i.e., soap and water plus alcohol) had the highest specificity (100%) and similar sensitivity (88%) compared with the other methods (sensitivity, 86% to 96%; specificity, 91% to 96%).

Key Question 3. What Are the Harms of Screening for Elevated BLLs (With or Without Screening Questionnaires) in Children?

As in the prior USPTF report, no studies evaluated the harms of screening versus not screening for elevated BLLs in children.

Key Question 4. Do Counseling and Nutritional Interventions, Residential Lead Hazard Control Techniques, or Chelation Therapy Reduce BLLs in Asymptomatic Children With Elevated BLLs?

Summary

One large, good-quality RCT included in the prior USPSTF review found that chelation therapy with DMSA in children with a mean blood lead concentration of 20 to 45 µg/dL was associated with decreased blood lead concentrations versus placebo at 1 week, 6 months, and 1 year, but there were no effects at longer-term followup at 4.5 to 6 years.[64-67] One fair-quality RCT included in the prior USPSTF review found no differences between chelation therapy versus placebo in blood lead concentration at 1 or 6 months.[68]

There was insufficient evidence from two poor-quality studies to determine effects of nutritional supplementation on BLLs. Three fair-quality RCTs from the United States and Australia (all included in the prior USPSTF review) found no clear effects of home lead remediation in lowering blood lead concentrations.

Evidence

The prior USPSTF review found that chelating agents may result in short-term reductions in blood lead concentrations in children but that reductions may not be sustained over longer periods in the absence of repeated or continuing chelation therapy or environmental interventions. Effects of cleaning, abatement, and education on blood lead concentrations were mixed, based on a descriptive summary of 11 studies. The prior USPSTF review also found conflicting evidence on the effects of nutritional interventional on elevated BLLs, based on a descriptive summary of 16 studies.

Seven RCTs[64-73] (reported in 10 publications) evaluated the effects of interventions to reduce blood lead concentrations in asymptomatic children with elevated BLLs (**Appendixes B3 and**

C2); four of the studies were included in the prior USPSTF review.[64-67,71,68] Two studies evaluated chelation therapy,[64-68] two studies evaluated counseling and nutritional interventions,[71,72] and three studies evaluated residential lead hazard control techniques.[69,70,73] Sample sizes ranged from 39 to 780 (total N=1,419). Five studies were conducted in the United States and one study each in Australia and Costa Rica. The mean age of study participants was 1.6 to 3.6 years and sex distribution was balanced in studies that provided this information (44% to 58% female). One study was rated good quality, four fair quality, and two poor quality. The poor-quality studies lacked descriptions of randomization methodology, allocation concealment, and masking, and one study had poor followup; the poor-quality studies were included because no fair- or good-quality studies were available.

Chelation

One fair-[68] and one good-quality[64-67] trial found inconsistent effects of DMSA chelation therapy on blood lead concentrations in asymptomatic children with BLLs of 20 to 45 µg/dL at baseline.[64-68] Although the good-quality trial found that chelation therapy was associated with lower blood lead concentrations versus placebo at 1 week, 6 months, and 1 year, it found no differences at 4 to 5.6 years. The fair-quality trial found no effect of chelation therapy on BLLs at 1 or 6 months. Both trials were included in the prior report.

The Treatment of Lead-Exposed Children (TLC) study, a good-quality RCT (n=780), evaluated 12- to 33-month-old children with blood lead concentration between 20 and 44 µg/dL.[64-67] All children received vitamin and mineral supplements and had home inspections with lead abatement. Children were randomized to treatment with DMSA (1,050 mg/m^2 per day for 7 days, then 700 mg/m^2 for 19 days) or placebo. Children could be treated with DMSA up to three times, with a goal blood lead concentration of less than 15 µg/dL. DMSA was associated with a mean difference in blood lead concentration at 1 week that was 11 µg/dL lower than placebo. However, blood lead concentrations increased once treatment was completed, and at 52 weeks the mean difference had decreased to 2.7 µg/dL in favor of DMSA (95% CI, 1.9 to 3.5 µg/dL).[67] In a followup study of 7-year-old participants (approximately 4.5 to 6 years after treatment), mean blood lead concentrations were identical in both groups (8.0 µg/dL).[65]

A small, fair-quality study (n=39)[68] randomized children ages 2.5 to 5 years with blood lead concentrations between 30 and 45 µg/dL to one course of DMSA or control. DMSA was dosed according to weight (≤15 kg, 100 mg dose; >15 kg, 200 mg dose), and each dose was administered three times a day for 5 days followed by twice a day for 14 days. There were no significant differences in mean blood lead concentrations at 1 month (27.4 µg/dL [standard deviation (SD), 7.5] vs. 33.2 µg/dL [SD, 10.3]; p=0.16) or at 6 months (28.8 µg/dL [SD, 6.4] vs. 25.1 µg/dL [SD, 6.8]; p=0.06).

Nutritional Interventions

Two poor-quality studies provided insufficient evidence to determine the effects of nutritional interventions on blood lead concentrations.[71,72] One double-blind, placebo-controlled trial conducted in New York City (n=88) that was included in the prior review evaluated the effects of calcium supplementation on blood lead concentrations but had high attrition (34%) and

inadequate descriptions of randomization, allocation concealment, and masking techniques.[71] The other study evaluated effects of iron supplementation in Costa Rican children[72] with elevated blood lead concentrations (mean, 10.98 µg/dL) at baseline. Results were difficult to interpret because iron supplementation was given to children who were iron depleted and placebo was given to children who were iron replete, with no matching on blood lead concentrations. Children were randomized to either intramuscular iron or oral iron. Iron was associated with a decrease in blood lead concentration in iron-deplete children and placebo was associated with slightly increased BLLs in iron-replete children, but it is unclear how baseline iron levels may have affected blood lead concentrations independent of iron supplementation. Another limitation of the trial is that results were reported for the subgroup of patients in the iron-deplete group who received oral iron, but not for those who received intramuscular iron.

Residential Lead Hazard Control Techniques

Three fair-quality RCTs found no clear effects of home lead abatement in lowering blood lead concentrations in asymptomatic children with elevated BLLs at baseline.[69,70,73] None of the studies were included in the prior review and home lead abatement interventions differed in each trial.

One trial (n=175) randomized children younger than age 28 months in Rhode Island with blood lead concentrations of 15 to 19 µg/dL[70] to a home intervention (five home visits that included testing samples, tailored education, and assessment of nutrition and parent-child interaction plus lead remediation strategies) or control intervention (one to two standard educational visits from an outreach worker). Blood lead concentrations in both groups decreased, but there was no significant difference between the intervention and control groups at 3, 6, or 12 months after baseline.

Another fair-quality trial (n=90)[69] conducted in Australia randomized pairs of 12- to 60-month-old children with mean blood lead concentrations between 15 and 30 µg/dL matched by age and BLL to home remediation and lead abatement versus delayed intervention for 1 year. Despite reductions in home lead concentrations after intervention, the effects of remediation on mean BLL were small (17.5 vs. 17.9 µg/dL; mean change, 1% [95% CI, -11% to 11%]), with no significant difference between groups.

A fair-quality trial (n=84)[73] conducted in Florida enrolled asymptomatic children from the WIC and Head Start programs and the local health department with blood lead concentrations of 3 to 10 µg/dL (mean, 5.29 µg/dL [range, 3.0 to 9.3 µg/dL]). Participants were randomized to receive an educational brochure, a home cleaning kit, a formal home inspection and remediation, or passive control. The educational brochure included information about diet, cleaning, and habits to reduce lead exposure. The home cleaning kit included a HEPA (high-efficiency particulate air) vacuum, trisodium phosphate detergent, gloves, rags, and buckets. The formal inspection/remediation group received a home risk assessment by a professional company that included dust wipe samples that were evaluated with on-site X-ray fluorescence spectrometry and laboratory testing. The inspection was followed by a second home visit and a written report with a range of optional steps on how to decrease lead exposure. The passive control group received no intervention or information. All groups experienced a decrease in blood lead

concentration of 2.26 to 2.99 µg/dL over 6 to 12 months, with no significant difference between groups.

Key Question 5. Do Counseling And Nutritional Interventions, Residential Lead Hazard Control Techniques, or Chelation Therapy Improve Health Outcomes in Asymptomatic Children With Elevated BLLs?

Summary

One good-quality randomized study included in the prior USPSTF review found no differences between chelation therapy versus placebo on neuropsychological outcomes despite a decrease in blood lead concentrations following chelation therapy.[65-67]

There was no evidence on effects of counseling and nutritional interventions or residential lead hazard control techniques on health outcomes in asymptomatic children with elevated blood lead concentrations at baseline.

Evidence

The prior USPSTF review found no clear evidence to support a clinical benefit from chelation therapy in children with elevated blood lead concentrations at baseline, based on one trial,[65-67] and found no studies on effects of environmental or nutritional interventions on health outcomes.

The TLC[65-67] trial (N=780) of DMSA chelation therapy versus placebo (see Key Question 4 for study details), included in the prior USPSTF review, was the only study to evaluate the effect of interventions for lowering elevated blood lead concentrations on health outcomes in children by measuring neuropsychological outcomes. At 36 months, there were no significant differences between chelation therapy and placebo in the Wechsler Preschool and Primary Scale of Intelligence-Revised, the Developmental Neuropsychological Assessment, or the Conners' Parent Rating Scale-Revised. In a followup study[65] of the same children at age 7 years (4.5 to 6 years after treatment), chelation therapy was associated with lower (worse) scores on the adjusted Attention and Executive Functions subscore of the Developmental Neuropsychological Assessment (unadjusted difference, -1.8 [95% CI, -4.5 to 1.0]; adjusted p=0.045). There were no statistically significant effects on any other cognitive, neuropsychiatric, or behavioral outcome.

We identified no new study on effects of chelation therapy, environmental interventions, or nutritional interventions on health outcomes. Evidence on the effects of interventions for lowering blood lead concentrations on health outcomes remains very limited.

Key Question 6. What Are the Harms of Interventions in Asymptomatic Children With Elevated BLLs?

Summary

One good-quality RCT[64,67]and one poor-quality observational study[74] reported adverse effects of chelation therapy. The good-quality RCT found that children treated with DMSA had a small but statistically significant decrease in height growth over 34 months and slightly poorer scores on attention and executive function tests at age 7 years (**Appendixes B3 and C2**).[65]

The poor-quality study reported adverse events associated with the less commonly used chelator d-penicillamine, including leukopenia, thrombocytopenia, urticarial and maculopapular rashes, urinary incontinence, abdominal pain, and diarrhea.[74]

No study evaluated harms of counseling, nutritional interventions, or residential lead hazard control techniques.

Evidence

The prior USPSTF report found adverse effects of environmental interventions including transient elevation in blood lead concentrations, inconvenience associated with abatement work or relocation, and cost-benefit considerations, but the number of studies on which these narrative findings was based was unclear. It also identified adverse effects after DMSA chelation therapy that included mild gastrointestinal (vomiting and diarrhea) and systemic symptoms, rashes, transient hyperphosphatasemia, neutropenia, eosinophilia, and elevations in serum aminotransferases. Most evidence from the prior report did not meet our inclusion criteria due to study design, lack of comparison group, wrong outcomes, or lack of a reference standard. The prior USPSTF review included data on harms from one good-quality RCT, which was also included in this update.

The TLC trial compared DMSA chelation therapy with placebo in children ages 12 to 33 months with blood lead concentrations between 20 and 44 µg/dL (N=780).[67] DMSA was associated with a small but statistically significant decrease in height growth over 34 months (difference of 0.35 cm [95% CI, 0.05 to 0.72 cm]) and slightly poorer scores on attention and executive function tests (unadjusted difference of -1.8; adjusted effect P=0.045) at age 7 years. There were no significant differences in laboratory values, including neutrophil count, platelet count, aminotransferase concentrations, and alkaline phosphatase concentration.[64,67] Children treated with DMSA were more likely to have evidence of minor traumatic injuries on physical examination (14.9% vs. 9.9%).[64] However, a mechanism for this association is not known or theorized.

A poor-quality retrospective cohort study (n=75) evaluated d-penicillamine in children with blood lead concentration of 25 to 40 µg/dL.[74] Twenty-nine adverse events were reported in 37 percent of study participants, including leukopenia (11%; white blood cell count <4,000/mm^3), rash (9%), low platelet count (9%; <300/mm^3), enuresis (4%), abdominal pain (3%), and

hematuria (1%) (**Appendix C3**). No study identified harms of counseling, nutritional interventions, or residential lead hazard control techniques.

Contextual Question 1. What Is the Reliability of Capillary and Venous BLL Testing at Various Lead Levels in Children?

Understanding whether current methods for testing for elevated BLLs is reliable would be helpful for confirming that a standard, predictable measure of blood lead exists and for informing testing strategies. We sought evidence to determine whether children are consistently classified as having elevated BLL at standard thresholds and whether tests perform reliably between laboratories and between patients across the minimum or standard threshold of BLLs. However, we found no studies on these aspects of reliability of BLL testing in children.

Contextual Question 2. What Is the Association Between Reduced BLLs and Improved Health Outcomes in Asymptomatic Children With Elevated BLLs?

One good-quality randomized study (in four publications) addressed the association between reduced BLLs and improved health outcomes in children with elevated BLLs. The previously described TLC study of chelation therapy with DMSA[65-67] (n=780) found an inverse relationship between cognitive test scores and changes in blood level concentration, with a decrease in cognitive test scores of 3.2 to 3.3 points for every 10-µg/dL increase in BLL. However, there was no correlation between short-term decreases in blood lead concentration and long-term cognitive test scores in the DMSA group compared with placebo.[66]

Contextual Question 3. Are There Valid Risk Prediction Tools Available That Identify Communities at Highest Risk for Lead Exposure That Could Be Used in Primary Care Practices to Target Screening Efforts in Children?

We identified no studies on the accuracy of community-level risk prediction tools for use in primary care screening to identify children at highest risk for lead exposure. Risk assessment tools for individuals are addressed in Key Question 1.

Chapter 4. Discussion

Summary of Review Findings

Consistent with the prior USPSTF review,[1] no study directly evaluated benefits or harms of screening children for elevated BLLs compared with no screening. As in the prior USPSTF review, we found four additional studies of instruments to identify children at higher risk of elevated BLLs to guide targeted screening, all of which had poor diagnostic accuracy. This update also confirms there are no clear effects of interventions for lowering elevated BLLs in affected children or for improving neurodevelopmental outcomes. Evidence reviewed for this update is summarized in **Table 2**.

Given the decreased prevalence of elevated BLLs in the U.S. pediatric population (from 88% between 1976 and 1980 to 0.8% from 2007 to 2010), targeted screening strategies have been suggested.[4] The most commonly used risk assessment instrument is the CDC questionnaire. However, studies found poor diagnostic accuracy of the 1991 CDC questionnaire for identifying children with elevated BLLs, with noninformative likelihood ratios.[3] In addition, the CDC questionnaire was created in 1991 and no study on its accuracy has been published since 1997, potentially limiting the applicability of currently available evidence to contemporary clinical practice. Accordingly, screening recommendations from the CDC, AAP, and other organizations note the limitations of this questionnaire. The CDC recommends that public and clinical health professionals collaborate to develop screening plans that are responsive to local conditions by using local data, with universal screening in the absence of such plans.[25,75] Accurate risk assessment instruments would facilitate improved targeted screening strategies, and some states have adapted the CDC questionnaire with items addressing local risk factors. However, studies on modified versions of the CDC questionnaire for specific settings and populations also showed poor accuracy for identifying children at risk for elevated BLLs.[48-51] In lieu of accurate screening instruments for identifying children to screen, alternative strategies such as universal screening[43,47] or screening targeted at communities with high prevalence of elevated BLLs could be effective.[44]

A recent systematic review[76] of screening questionnaires for elevated BLLs reported sensitivities ranging from 0.25 to 0.87 and specificities ranging from 0.31 to 0.80, but it included other questionnaires, did not report results for the CDC questionnaire separately, included studies that evaluated different cutoffs for a positive questionnaire, or did not use venous samples as the reference standard. Our findings regarding the poor accuracy of the CDC questionnaire are generally consistent with this review.

Four studies evaluated the diagnostic accuracy of capillary blood lead testing compared with venous measurement.[27,61-63] Capillary sampling is slightly less sensitive than venous sampling, with comparable specificity, provided that contamination is avoided using standard techniques. Factors that may inform the decision to perform capillary versus venous sampling for screening include the tradeoffs between slightly worse accuracy and greater convenience or patient preferences. Both methods require confirmation of elevated BLLs. The prior review provided descriptive information of some diagnostic tests but did not evaluate the diagnostic accuracy of

sampling techniques using venous blood as a reference standard.

There is limited evidence on the effectiveness of interventions for elevated BLLs on neurodevelopmental outcomes and BLLs. One trial showed short-term (through 1 year) effects of DMSA chelation therapy on lowering BLLs versus placebo in children with moderately elevated BLLs (20 to 44 µg/dL) at baseline, but no clear effects on longer-term BLLs or neurodevelopmental outcomes, and some data indicating potential harms (hematological and other laboratory parameters and growth).[64-67] A small, fair-quality trial found no effects of DMSA chelation therapy on BLLs.[68] No trial evaluated effects of chelation therapy in children with BLLs less than 20 µg/dL, but chelation therapy in children with blood lead concentrations in this range is not recommended in the absence of severe symptoms. Evidence on residential interventions was limited and showed no clear effects on blood lead concentrations, while evidence on nutritional interventions (calcium or iron supplementation) was of poor quality and insufficient to determine effects on clinical outcomes. The prior review found limited and contradictory effects of nutritional interventions, no studies on outcomes related to residential lead hazard control, and short term reductions in BLL from chelation therapy, with no sustained effect over longer periods.

Contextual Issues

Evidence on the intraindividual and interlaboratory reliability of BLL testing would be helpful for interpreting testing results, informing technical standards, and informing testing protocols and strategies. Newer recommendations suggest the use of a population-based reference value as the "level of concern" to identify children and environments associated with lead hazards.[77] Lowering the reference value may affect the accuracy and precision of blood collection and analysis, suggesting that further evidence on test reliability would be advantageous. The World Health Organization has noted the potential benefits of portable point-of-care testing and recommends a highly accurate method with a low limit of detection for the general population in which relatively low levels of exposure exist.[78] The association between reduced BLLs and improved health outcomes was addressed in one treatment trial, which found that short-term decreases in blood lead concentrations induced by treatment with DMSA did not correlate with long-term cognitive test scores.[66]

Limitations

This review has several limitations. First, there was an overall lack of evidence to address all Key Questions. Second, despite searching for updated data, the available studies evaluating the effectiveness of risk-based questionnaires were published between 1994 and 2003 and may not assess contemporary risk factors. Current clinical practice uses a reference BLL of greater than 5 µg/dL, based on updated CDC guidance, but several of the studies included in this review used the older reference value of 10 µg/dL. Despite changing reference values, included studies of diagnostic accuracy may also not reflect the amount of potential error in measures of continuous BLLs, as these are prone to miscategorization due to the dichotomization of results, regardless of which threshold is used. Third, nonrandomized studies were included to evaluate the

effectiveness of interventions for elevated BLLs, but these are more susceptible to confounding and bias than well conducted RCTs, leading to downgrading of study quality. Fourth, direct correlation of environmental lead exposures with longer-term health outcomes is difficult to study and characterize, since these exposures often have subtle clinical effects. Fifth, the review focused on screening and treatment of individuals in primary care settings, excluding community and public health approaches that could inform screening practices at the population level. The review restricted inclusion to English-language articles, which could result in language bias. However, we did not identify non–English-language studies in our searches that otherwise met inclusion criteria. Finally, we did not attempt meta-analysis for outcomes other than diagnostic accuracy, given the small number of studies and clinical and methodological diversity within the studies, and we were unable to formally assess for publication bias due to the small number of studies.

Evidence for Priority Populations, Particularly Racial/Ethnic Minorities

Elevated BLLs predominantly affect socioeconomically disadvantaged and minority children. Different sources of lead exposure than previously considered are emerging in these populations, yet research on screening and prevention in these populations remains limited.[79-81] Exposures related to community water sources, lead pipes in schools, and factory emissions affecting neighborhood soil quality are some of the emerging factors that are not well incorporated into current screening questionnaires. Additional research is warranted to validate these potential associations in specific geographic locations and among at-risk populations. Culturally-linked sources of lead poisoning such as imported candy, pottery, and cosmetics, specific to subpopulations living in the United States, may also provide information about risk in minority populations. For example, traditional folk remedies and imported digestive remedies that may contain high levels of lead are not monitored by the U.S. Food and Drug Administration and are more common in Hispanic and Asian populations.[80,81] Nontraditional sources of lead exposure that come from items manufactured in other countries, such as leaded pots and pans, cosmetics, medicines, ceramics, candy, and leaded crystal may also pose additional risk since little regulation exists to monitor, identify, and control these nonpaint exposures. Children who are exposed to less commonly recognized sources of lead exposure also often live in areas with a higher risk for housing-related source exposures.[79] The dual risk associated with minority communities calls for a more focused strategy to deal with population-specific risks.

Future Research

Elevated BLLs are associated with serious health consequences. Additional research is needed to better inform decisions regarding screening for elevated BLLs in children. Effective screening could identify lead-contaminated residential environments and abate them, not only to improve the health of the child but also for siblings and others in the household. While remediation of lead exposures in a specific residence may be too late for a child who already is exposed, interventions could prevent exposures in subsequent generations of children who may reside in that residence. Development of questionnaires that incorporate current risk factors for elevated

BLLs with validation in contemporary populations of children in the United States is necessary. Research is needed to evaluate the effectiveness of treatments for elevated BLLs such as counseling, nutritional interventions (such as calcium), and residential lead hazard control techniques in trials with adequate sample sizes to inform treatment strategies. While there is limited evidence for a clinical benefit of nutritional supplementation in reducing BLLs in children, epidemiological evidence is supported by studies of the toxicokinetics of lead in childhood[82] and could be further validated by well-designed research studies. Ideally, randomized trials would recruit children from a range of racial/ethnic and socioeconomic strata, and evaluate the effects of screening on improving health outcomes as well as harms in the short and long term. However, randomized trials may not be feasible or appropriate for lead screening or some interventions of environmental health exposures due to ethical issues. Research on newer methods for testing for elevated BLLs, such as point-of-care testing, and on the intraindividual and interlaboratory reliability of BLL testing would be helpful for informing testing strategies.

Conclusions

Evidence on the benefits and harms of screening children for lead poisoning is lacking. Screening questionnaires are not accurate for identifying children with elevated BLLs. Capillary blood testing is slightly less accurate than venous blood testing for identification of elevated BLLs. Treatment studies of chelating agents, often combined with environmental or household interventions, were not associated with sustained effects on BLLs but were associated with harms.

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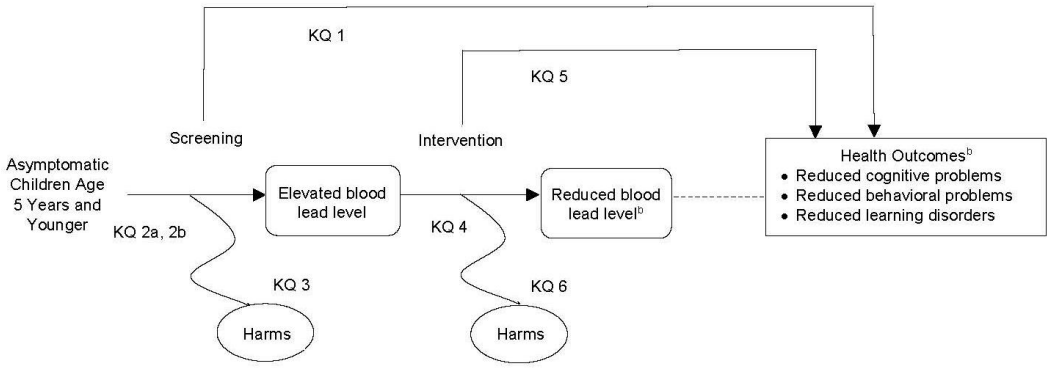
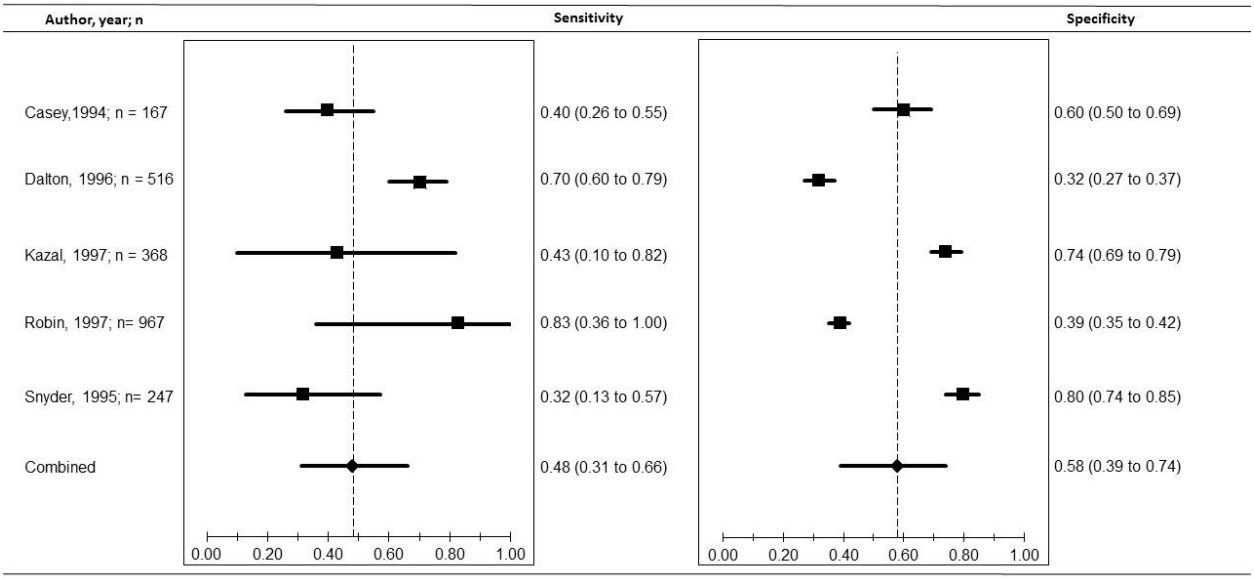
Figure 1. Analytic Framework and Key Questions



Abbreviation: KQ=key question.

[a] Interventions include counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy.
[b] We included outcomes measured in family members (e.g., siblings, pregnant women in the same household) subsequently identified as having elevated blood lead levels after the index family member was found to have an elevated blood lead level during screening.

Figure 2. Sensitivity and Specificity of CDC Screening Questionnaire (>1 Positive Answers and >10 µg/dL Venous BLL)



Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention.

Table 1. Current Recommendations From Other Organizations

Organization, Year	Screening Recommendation
American Academy of Family Physicians (AAFP) 2006[36]	The AAFP adopted the 2006 USPSTF recommendations for children. Recommendations state that evidence is insufficient to recommend for or against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at increased risk. The AAFP recommends against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at average risk.
American Academy of Pediatrics (AAP) 2016[37]	Providers should test asymptomatic children for elevated blood lead concentrations according to federal, local, and state requirements. Immigrant, refugee, and internationally adopted children also should be tested for blood lead concentrations when they arrive in the United States due to increased risk. Recommends targeted screening of children ages 12 to 24 months living in communities with ≥25% of housing built before 1960 or a prevalence of BLLs ≥5 µg/dL of ≥5%; children who live in or visit a home or child care facility with an identified lead hazard; and children living in a home built before 1960 in poor repair or renovated in the past 6 months.
American Academy of Pediatrics (AAP)/ Bright Futures[35] 2012	Screening for lead poisoning should be done in accordance with state law as applicable. For children who live in states that do not have a state screening program in place, the AAP recommends universal screening for children at ages 12 and 24 months.
American College of Preventive Medicine (ACPM) 2001[33]	Screening for elevated BLLs via venous or capillary blood lead testing should be conducted for children at age 1 year, only if they are identified as being at high risk for elevated BLLs. Criteria for being at high risk include receipt of Medicaid or WIC, living in a community with ≥12% prevalence of BLLs at ≥10 µg/dL, living in a community with ≥27% of homes built before 1950, or meeting one or more high-risk criteria of a lead screening questionnaire. This questionnaire should include both questions suggested by the CDC in its 1997 guidelines and questions developed for and tailored to specific communities. These questions may pertain to use of home remedies and cosmetics, country of origin, and behavioral risk factors. Risk assessment for lead exposure should be performed beginning during prenatal visits and continuing until age 6 years.
Centers for Disease Control and Prevention (CDC) 2010[23]	Guidelines emphasize primary prevention of lead poisoning and recommend that clinicians educate families about prevention of lead exposure and provide environmental assessments to identify sources of lead exposure before testing children for lead poisoning.
Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) 2012[4]	Blood lead screening remains necessary to identify children for whom primary prevention is unsuccessful. Screening for lead poisoning should be done in accordance with state law as applicable. For children who live in states that do not have a state screening program in place, the ACCLPP recommends universal screening for children at ages 12 and 24 months.

Abbreviations: AAFP=American Academy of Family Physicians; AAP=American Academy of Pediatrics; ACCLPP=Advisory Committee on Childhood Lead Poisoning Prevention; ACPM=American College of Preventive Medicine; BLL=blood lead level; CDC=Centers for Disease Control and Prevention; USPSTF=U.S. Preventive Services Task Force.

Table 2. Summary of Evidence

Key Question*	Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Strength of Evidence†
1	No studies	0	No studies	No studies	Not applicable	No studies	Insufficient
2a	Not previously reviewed‡	10 cross-sectional studies	All studies conducted from 1994 to 2003; studies used the 1991 CDC questionnaire or a modified version of this survey.	Consistent	Moderate	Five studies that used the threshold of ≥1 positive answers on the 5-item 1991 CDC screening questionnaire reported a pooled sensitivity of 48% (95% CI, 31.4% to 65.6%) and specificity of 58% (95% CI, 39.9% to 74.0%) for identifying children with a venous BLL ≥10 µg/dL. Four studies that used versions of the CDC questionnaire modified for specific populations or settings did not demonstrate improved accuracy (sensitivity range, 25% to 68%; specificity range, 49% to 58%).	Moderate
2b	Not previously reviewed‡	4 observational studies	None	Consistent	Moderate	Four studies conducted in urban areas of the U.S. found capillary BLL testing associated with sensitivity of 87% to 91% and specificity >90% (92% to 99%) for identification of elevated BLL compared with venous sampling.	Moderate
3	No studies	0	No studies	No studies	Not applicable	No studies	Insufficient
4	Not previously reviewed‡	7 RCTs or observational studies (in 10 publications)	Poor-quality studies of nutritional interventions do not provide adequate data to assess treatment effects.	Consistent	Low to moderate	One large RCT found that chelation therapy with DMSA in children with a mean BLL of 20 to 45 µg/dL was associated with decreased BLL vs. placebo at 1 week, 6 months, and 1 year, but there were no effects at longer-term followup at 4.5 to 6 years. One RCT found no differences between chelation and placebo in BLL at 1 or 6 months. There was insufficient evidence from 2 studies to determine effects of nutritional supplementation. Three studies of residential lead hazard control techniques found no difference in BLL between intervention or control groups.	Moderate

Table 2. Summary of Evidence

Key Question*	Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Strength of Evidence†
5	No clear evidence to support a clinical benefit from chelation therapy in children with elevated BLL at baseline, based on 1 trial; no studies on effects of environmental or nutritional interventions on health outcomes.	1 RCT (in 3 publications)	Based on 1 RCT of 780 U.S. children, the adjusted treatment effect on one cognitive testing subscore showed a statistically significant but small improvement in the placebo group (p=0.045). No other significant outcomes for all other effects of treatment on cognitive, neuropsychiatric, and behavioral testing scores.	Consistent	Moderate	One randomized study found no differences between chelation therapy and placebo in neuropsychological outcomes, despite a decrease in BLL following chelation. There was no evidence on effects of counseling and nutritional interventions or residential lead hazard control techniques on health outcomes in asymptomatic children with elevated BLL at baseline.	Moderate

Table 2. Summary of Evidence

Key Question*	Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Strength of Evidence†
6	Adverse effects of environmental interventions included transient BLL, inconvenience associated with abatement work or relocation, and cost-benefit considerations. Adverse effects after chelation treatment included mild GI and systemic symptoms, rashes, transient hyperphosphatas-emia, neutropenia, eosinophilia, and elevations in serum aminotransferases	1 RCT (in 3 publications) and 1 observational study	One poor-quality study reported intermediate outcomes associated with adverse effects of treatment.	Consistent	Moderate to high for harms	One good-quality and 1 poor-quality study reported adverse effects of chelation therapy. The good-quality study found that children treated with DMSA had a small but statistically significant decrease in height growth over 34 months and slightly poorer scores on attention and executive function tests at age 7 years. One poor-quality study reported adverse events associated with the less commonly used chelator d-penicillamine, including leukopenia, thrombocytopenia, urticarial and maculopapular rashes, urinary incontinence, abdominal pain, and diarrhea. No study identified harms of counseling, nutritional interventions, or residential lead hazard control techniques.	Moderate

* Key Question 1. Is there direct evidence that screening for elevated BLLs in asymptomatic children age 5 years and younger improves health outcomes (i.e., reduced cognitive or behavioral problems or learning disorders)?
Key Question 2a. What is the accuracy of questionnaires or clinical prediction tools that identify children who have elevated BLLs?
Key Question 2b. What is the accuracy of capillary blood lead testing in children?
Key Question 3. What are the harms of screening for elevated BLLs (with or without screening questionnaires) in children?
Key Question 4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs in asymptomatic children with elevated BLLs?
Key Question 5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated BLLs?
Key Question 6. What are the harms of interventions in asymptomatic children with elevated BLLs?
† "EPC Assessment of Strength of Evidence" is based on new evidence identified for this update and relevant evidence from the prior report.
‡ Key Questions in this review differ from the previous review and Key Question numbers in this review do not correspond to Key Question numbers in the prior review. For some questions, the number of studies included in the prior review was not precisely reported.

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DMSA=dimercaptosuccinic acid; GI=gastrointestinal; RCT=randomized, controlled trial; U.S.=United States; USPSTF=U.S. Preventive Services Task Force.

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion With Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Casey, 1994[43] United States Urban general pediatric department Fair	CDC Risk Assessment Questionnaire ≥1 positive answers	n=167 Elevated BLL: Overall ≥10 µg/dL: 29% (48/165) 10 to 14 µg/dL: 22% (36/165) 15 to 19 µg/dL: 4% (7/165) 20 to 44 µg/dL: 2.5% (4/165) 46 µg/dL: 0.5% (1/165) Low-risk vs. high-risk Mean age, months: 10 vs. 9 Female: 50% vs. 50% Ethnicity: 29% vs. 33% African American 62% vs. 62% White	Overall: 40% (19/48 [95% CI, 25.77 to 54.73]) By screening question: Peeling paint: 15% Renovation: 31% Sibling with Pb: 6% Adult's job with Pb: 2% Live near Pb industry: 6%	Overall: 60% (70/117 [95% CI, 50.36 to 68.78%]) By screening question: Peeling paint: 76% Renovation: 75% Sibling with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%
Dalton, 1996[44] United States Medical center Fair	CDC Risk Assessment Questionnaire Additional behavioral risk factor questions ≥1 positive or equivocal answers	n=516 Elevated BLL: Overall ≥10 µg/dL: 22% (101/463) ≥15 µg/dL: 6% (28/463) Mean age, months: NR (range, 6 to 72) Female: NR Ethnicity: NR	<u>CDC Risk Factors</u> Overall: 70.3% (95% CI, 60.39 to 78.98) <u>Behavioral Risk Factors</u> Playing near outside of house: 74.2% (95% CI, 64.60 to 82.44)	<u>CDC Risk Factors</u> Overall: 31.8% (95% CI, 27.00 to 36.84) <u>Behavioral Risk Factors</u> Playing near outside of house: 54.1% (95% CI, 28.05 to 37.98)
France, 1996[48] United States Multisite primary care network Fair	CDC Risk Assessment Questionnaire Additional risk factor questions ≥1 positive or equivocal answers	n=2,978 Mean BLL: 4.19 µg/dL Elevated BLL ≥10 µg/dL: 2.9% (85/2,978) Mean age: NR (range, 5 months to 6.5 years) Female: NR Ethnicity: NR	CDC + additional questions: 59.7% (95% CI, 48 to 72) CDC alone: 57% (95% CI, 45 to 69)	CDC + additional questions: 36% (95% CI, 34 to 38) CDC alone: 51% (95% CI, 49 to 53)

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion With Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Holmes, 1997[49] United States Continuity clinic at a children's hospital Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=754 Elevated BLL ≥10 µg/dL: 3.1% (25/801)	68% (95% CI, 46.50 to 85.05)	58% (95% CI, 53.93 to 61.23)
Kazal, 1997[47] United States Rural clinic on a Navajo Reservation Fair	CDC Risk Assessment Questionnaire Additional risk factor questions Unclear definition of positive screening exam	n=368 Elevated BLL ≥10 µg/dL: 2.2% (8/368) Mean age, months: 30.5 Female: 49% Ethnicity: 98% Navajo	CDC questions: 42.9% (95% CI, 9.90 to 81.59) CDC + additional questions: 42.9% (95% CI, NR)	CDC questions: 68.52% (95% CI, 68.52 to 78.50) CDC + additional questions: 66.1% (95% CI, NR)
Muniz, 2003[50] United States Rural clinic Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=171 Elevated BLL ≥10 µg/dL: 2.3% (4/171) Mean age: NR (range, 9 to 24 months) Female: NR Ethnicity: NR	CDC questions: 25% (95% CI, NR) CDC + additional questions: 50.0% (95% CI, 6.76 to 93.24)	CDC questions: 49% (95% CI, NR) CDC + additional questions: 49.70% (95% CI, 41.88 to 57.53)
Robin, 1997[45] United States Urban and rural Medicaid recipients Fair	Modified Health Care Financing Administration questionnaire	n=967 Elevated BLL ≥10 µg/dL: 0.6% (6/967) Mean age: NR (range, 2 to 6 years) Female: 51.3% Ethnicity: Alaska native: 60% White: 28% Black: 5%	83.3% (95% CI, 35.88 to 99.58)	38.6% (95% CI, 35.50 to 41.77)
Schaffer, 1996[51] United States Rural clinic Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=705 Elevated BLL ≥10 µg/dL: 8.4% (59/705) Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR	CDC + additional questions: 75% (95% CI, NR) Condensed questionnaire from 4 items most likely to correctly identify patients: 88% (95% CI, NR)	CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion With Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Snyder, 1995[46] United States Public clinics Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=247 Elevated BLL ≥10 µg/dL: 7.7% (19/247) Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR	CDC questions: 31.6% (95% CI, 12.58 to 56.55) Additional questions: 89.5% (95% CI, 66.86 to 98.70) CDC + additional questions: 89.5% (95% CI, 66.6 to 98.70)	CDC questions: 79.8 (95% CI, 74.02 to 84.83) Additional questions: 37.3% (95% CI, 30.99 to 43.91) CDC + additional questions: 31.6% (95% CI, 25.6 to 38.0)

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; NR=not reported; Pb=lead.

Screening

Database: Ovid MEDLINE (R) 1946 to March Week 2, 2017

1 exp Lead/
2 exp Lead Poisoning/
3 1 or 2
4 exp mass screening/
5 exp "Surveys and Questionnaires"/
6 exp risk/
7 4 or 5 or 6
8 3 and 7
9 limit 8 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
10 exp pregnancy/
11 exp pregnancy complications/
12 exp fetus/
13 exp prenatal care/
14 exp Prenatal Exposure Delayed Effects/
15 exp Prenatal Injuries/
16 exp "Embryonic and Fetal Development"/
17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 8 and 17
19 9 or 18
20 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21 19 or 20
22 exp diagnosis/
23 3 and 22
24 17 and 23
25 limit 24 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
26 24 or 25
27 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp.
28 17 and 27
29 limit 27 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
30 28 or 29
31 26 or 30
32 21 or 31
33 limit 32 to humans
34 limit 33 to english language
35 limit 33 to abstracts
36 34 or 35

37 remove duplicates from 36
38 limit 37 to yr="2002 -Current"
39 limit 37 to yr="1902-2001"

Treatment

Database: Ovid MEDLINE (R) 1946 to March Week 2, 2017

1 exp Lead Poisoning/dh, dt, nu, su, th [Diet Therapy, Drug Therapy, Nursing, Surgery, Therapy]
2 exp Lead/ae, to [Adverse Effects, Toxicity]
3 ((treat* or therap* or interven* or counsel* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.
4 exp Lead Poisoning/ or exp Lead/
5 3 and 4
6 1 or 5
7 exp Therapeutics/
8 (th or dt or dh).fs.
9 exp counseling/
10 exp health education/
11 7 or 8 or 9 or 10
12 4 and 11
13 6 or 12
14 limit 13 to humans
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16
18 remove duplicates from 17
19 limit 18 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
20 exp Pregnancy/
21 exp Pregnancy Complications/
22 exp fetus/
23 exp prenatal care/
24 exp Prenatal Exposure Delayed Effects/
25 exp Prenatal Injuries/
26 exp "Embryonic and Fetal Development"/
27 20 or 21 or 22 or 23 or 24 or 25 or 26
28 14 and 27
29 19 or 28
30 18 not 29

Screening and Treatment

Database: Cochrane Database of Systematic Reviews 2005 to April 19, 2017

1 ((treat* or therap* or interven* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.

2 ((screen* or ((routin* or annual* or yearly) adj5 (test* or diagnos* or assay* or exam*))) adj7 ((lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*)))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2

Database: EBM Reviews - Cochrane Central Register of Controlled Trials through March 2017

1 ((treat* or therap* or interven* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.
2 ((screen* or ((routin* or annual* or yearly) adj5 (test* or diagnos* or assay* or exam*))) adj7 ((lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*)
3 1 or 2

Appendix A2. Inclusion and Exclusion Criteria

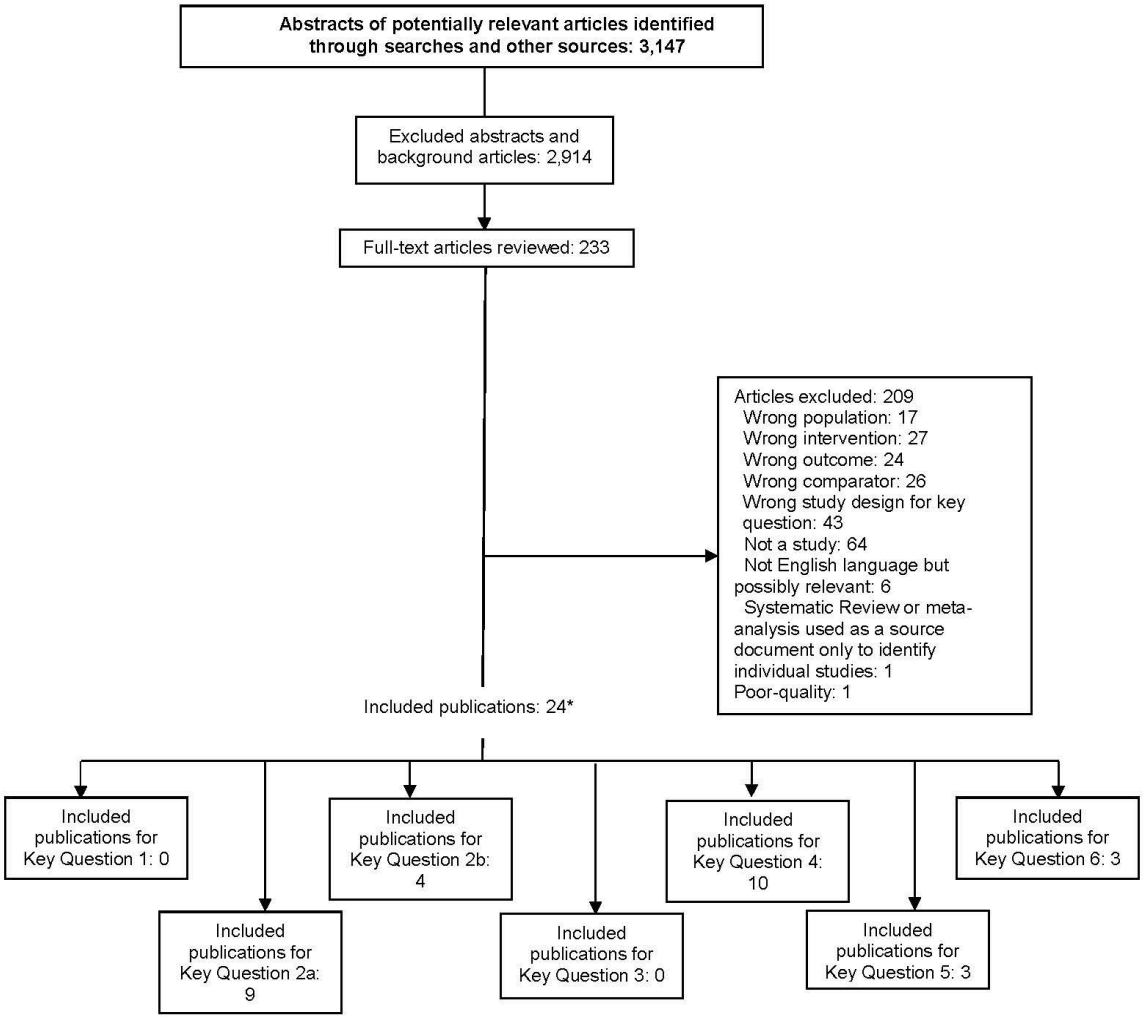
	Include	Exclude
Populations	**All KQs:** Asymptomatic children age ≤5 years	All other populations*
Screening tests	**KQs 1, 3:** Measurement of blood lead level (using any method) with or without screening questionnaires or risk prediction tools **KQ 2a:** Questionnaires or risk prediction tools that identify children who are more or less likely to have elevated blood lead levels (defined by a minimum threshold of 5 µg/dL) **KQ 2b:** Measurement of BLLs using capillary blood sampling	All other screening tests, including point-of-care blood lead level assays that are not approved by the U.S. Food and Drug Administration and are not available in the United States
Interventions	**KQs 4–6:** Studies assessing interventions aimed at reducing blood lead levels, including one or more of the following: counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy	Policies, laws, or community-based interventions focused on the primary prevention of lead exposure
Comparisons	**KQs 1, 3:** Screened vs. nonscreened groups **KQ 2a:** Measurement of blood lead levels using venous blood sampling **KQ 2b:** Studies on accuracy of capillary sampling to detect elevated blood lead levels must include a comparison with venous sampling **KQs 4–6:** Treatment vs. placebo, inactive control, or no treatment	All other comparisons, including head-to-head comparisons of two different interventions
Outcomes	**KQs 1, 5:** Validated measures of cognitive and neurobehavioral outcomes in children, including assessment of IQ or development† **KQ 2a:** Sensitivity, specificity, discrimination, and calibration **KQ 2b:** Sensitivity, specificity, discrimination, calibration and measures of diagnostic accuracy **KQ 3:** Anxiety, distress, pain, or discomfort related to venous or capillary blood sampling; false-positive results or blood lead levels <5 µg/dL, leading to repeat testing, unnecessary treatment, or both **KQ 4:** Blood lead levels† **KQ 6:** Anxiety or distress; inconvenience associated with intervention (e.g., school absenteeism associated with followup testing); morbidity attributed to chelation therapy (e.g., renal toxicity, sensitivity reactions)	All other outcomes, including measures of household lead dust
Study designs	**KQs 1, 4:** RCTs **KQ 2a:** Observational studies assessing the accuracy of screening questionnaires for predicting elevated blood lead levels **KQ 2b:** Observational studies assessing the accuracy of capillary sampling to measure blood lead levels **KQ 3:** RCTs, CCTs, and cohort studies **KQ 5:** RCTs and CCTs **KQ 6:** RCTs, CCTs, prospective cohort studies with a concurrent control group, and case-control studies	Systematic reviews,‡ case series, case reports, or comparison with historical controls
Quality	Studies rated good or fair quality	Studies rated poor quality
Clinical Setting	Settings applicable to U.S. primary care settings, including pediatric outpatient clinics, community health clinics, and school-based clinics **KQs 4–6:** The above plus settings referable from primary care settings	All other settings, including community health case-finding (e.g., blood lead level monitoring after known environmental exposure)
Country Setting	**KQs 1-3:** Research conducted in the United States or in populations similar to U.S. populations with services and interventions applicable to U.S. practice (i.e., countries with a United Nations Human Development Index of "very high" or "high" when no other evidence is available) **KQs 4–6:** Any country	**KQs 1–3:** Research not relevant to the United States or conducted in countries with a Human Development Index other than "very high"
Language	English language	Languages other than English

Abbreviations: CCT=controlled clinical trial; IQ=intelligence quotient; KQs=Key Questions; RCT=randomized, controlled trial; U.S.=United States.

Appendix A2. Inclusion and Exclusion Criteria

* Studies enrolling older children were eligible if at least 50% of the sample was age ≤5 years, or if studies report outcomes separately for children age ≤5 years.
† We included outcomes measured in family members (e.g., siblings, pregnant women in the same household) subsequently identified as having elevated blood lead levels after the index family member was found to have an elevated blood lead level during screening.
‡ Systematic reviews were excluded from the evidence review. However, we conducted a separate search to identify relevant systematic reviews published since the last review to ensure that our database searches have captured all relevant studies. We describe relevant systematic reviews in the Discussion section of the report.

Appendix A3. Literature Flow Diagram



* Other sources include prior reports, targeted searches for contextual questions, reference lists of relevant articles, and systematic reviews. Publications may be included for more than one Key Question.

Appendix A4. List of Included Studies

1. Anonymous. Safety and efficacy of succimer in toddlers with blood lead levels of 20-44 microg/dL. Treatment of Lead-Exposed Children (TLC) Trial Group. Pediatr Res. 2000;48(5):593-9. doi: 10.1203/00006450-200011000-00007. PMID: 11044477.
2. Boreland F, Lesjak M, Lyle D. Evaluation of home lead remediation in an Australian mining community. Sci Total Environ. 2009;408(2):202-8. doi: 10.1016/j.scitotenv.2009.10.013. PMID: 19853886.
3. Brown MJ, McLaine P, Dixon S, et al. A randomized, community-based trial of home visiting to reduce blood lead levels in children. Pediatrics. 2006;117(1):147-53. doi: 10.1542/peds.2004-2880. PMID: 16396872.
4. Casey R, Wiley C, Rutstein R, et al. Prevalence of lead poisoning in an urban cohort of infants with high socioeconomic status. Clin Pediatr. 1994;33(8):480-4. PMID: 7955789.
5. Dalton MA, Sargent JD, Stukel TA. Utility of a risk assessment questionnaire in identifying children with lead exposure. Arch Pediatr Adolesc Med. 1996;150(2):197-202. PMID: 8556126.
6. Dietrich KN, Ware JH, Salganik M, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics. 2004;114(1):19-26. PMID: 15231903.
7. France EK, Gitterman BA, Melinkovich P, et al. The accuracy of a lead questionnaire in predicting elevated pediatric blood lead levels. Arch Pediatr Adolesc Med. 1996;150(9):958-63. PMID: 8790128.
8. Holmes SE, Drutz JE, Buffone GJ, et al. Blood lead levels in a continuity clinic population. J Toxicol Clin Toxicol. 1997;35(2):181-6. PMID: 9120888.
9. Holtrop TG, Yee HY, Simpson PM, et al. A community outreach lead screening program using capillary blood collected on filter paper. Arch Pediatr Adolesc Med. 1998;152(5):455-8. PMID: 9605028.
10. Kazal LA, Jr. The failure of CDC screening questionnaire to efficiently detect elevated lead levels in a rural population of children. J Fam Pract. 1997;45(6):515-8. PMID: 9420588.
11. Liu X, Dietrich KN, Radcliffe J, et al. Do children with falling blood lead levels have improved cognition? Pediatrics. 2002;110(4):787-91. PMID: 12359796.
12. Markowitz ME, Sinnett M, Rosen JF. A randomized trial of calcium supplementation for childhood lead poisoning. Pediatrics. 2004;113(1 Pt 1):e34-9. PMID: 14702492.
13. Muniz MA, Dundas R, Mahoney MC. Evaluation of a childhood lead questionnaire in predicting elevated blood lead levels in a rural community. J Rural Health. 2003;19(1):15-9. PMID: 12585770.
14. Nicholson JS. A community-based intervention for low-income families to reduce children's blood lead levels between 3–9.9 μg/Dl. Children's Health Care. 2017:1-18. doi: 10.1080/02739615.2017.1370673.
15. O'Connor ME, Rich D. Children with moderately elevated lead levels: is chelation with DMSA helpful? Clin Pediatr (Phila). 1999;38(6):325-31. doi: 10.1177/000992289903800602. PMID: 10378089.
16. Parsons PJ, Raciti K, Esernio-Jenssen D. Evaluation and improvement of sample collection procedures for the determination of blood lead Center for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention: 1993.
17. Robin LF, Beller M, Middaugh JP. Statewide assessment of lead poisoning and exposure risk among children receiving Medicaid services in Alaska. Pediatrics. 1997;99(4):E9. PMID: 9099784.
18. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001;344(19):1421-6. doi: 10.1056/NEJM200105103441902. PMID: 11346806.
19. Sargent JD, Dalton MA. Rethinking the threshold for an abnormal capillary blood lead screening test. Arch Pediatr Adolesc Med. 1996;150(10):1084-8. PMID: 8859143.

Appendix A4. List of Included Studies

20. Schaffer SJ, Kincaid MS, Endres N, et al. Lead poisoning risk determination in a rural setting. Pediatrics. 1996;97(1):84-90. PMID: 8545231.
21. Schlenker TL, Fritz CJ, Mark D, et al. Screening for pediatric lead poisoning. Comparability of simultaneously drawn capillary and venous blood samples. JAMA. 1994;271(17):1346-8. PMID: 8158820.
22. Shannon M, Graef J, Lovejoy FH, Jr. Efficacy and toxicity of D-penicillamine in low-level lead poisoning. J Pediatr. 1988;112(5):799-804. PMID: 3361395.
23. Snyder DC, Mohle-Boetani JC, Palla B, et al. Development of a population-specific risk assessment to predict elevated blood lead levels in Santa Clara County, California. Pediatrics. 1995;96(4 Pt 1):643-8. PMID: 7567324.
24. Tejeda DM, Wyatt DD, Rostek BR, et al. Do questions about lead exposure predict elevated lead levels? Pediatrics. 1994;93(2):192-4. PMID: 8121730.
25. Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. J Pediatr. 2003;143(6):789-95. doi: 10.1067/S0022-3476(03)00540-7. PMID: 14657829.

Appendix A5. List of Excluded Studies

1. Abendroth K. [Excellent effect of sodium-citrate-EDTA-combination therapy in severe lead poisoning during pregnancy]. Dtsch Gesundheitsw. 1971;26(45):2130-1. PMID: 5004297. Excluded: Not English language, but possibly relevant.
2. Alfaro C, Vincelet C, Lombrail P, et al. [Evaluation of the screening strategy for lead poisoning in 1-to-3-year-old children monitored in maternal-child welfare centers in Paris]. Rev Epidemiol Sante Publique. 1993;41(6):473-9. PMID: 8296033. Excluded: Not English language, but possibly relevant.
3. Alpert JJ. Screening for lead poisoning. Pediatrics. 1970;45(4):721-2. PMID: 5438185. Excluded: Not a study.
4. Altmann P, Maruna RF, Maruna H, et al. [Lead detoxication effect of a combined calcium phosphate and ascorbic acid therapy in pregnant women with increased lead burden (author's transl)]. Wien Med Wochenschr. 1981;131(12):311-4. PMID: 7293190. Excluded: Not English language, but possibly relevant.
5. Anderson MK, Amrich M, Decker KL, et al. Using state lead poisoning surveillance system data to assess false positive results of capillary testing. Matern Child Health J. 2007;11(6):603-10. doi: 10.1007/s10995-007-0196-1. PMID: 17340181. Excluded: Wrong study design for Key Question.
6. Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: a review of epidemiologic studies. Am J Ind Med. 1994;26(1):13-32. PMID: 8074121. Excluded: Not a study.
7. Anonymous. The Treatment of Lead-exposed Children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatr Perinat Epidemiol. 1998;12(3):313-33. PMID: 9690266. Excluded: Not a study.
8. Arbuckle TE, Liang CL, Morisset AS, et al. Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. Chemosphere. 2016;163:270-82. doi: 10.1016/j.chemosphere.2016.08.023. PMID: 27540762. Excluded: Wrong study design for Key Question.
9. Aschengrau A, Beiser A, Bellinger D, et al. The impact of soil lead abatement on urban children's blood lead levels: phase II results from the Boston Lead-In-Soil Demonstration Project. Environ Res. 1994;67(2):125-48. doi: 10.1006/enrs.1994.1069. PMID: 7982389. Excluded: Wrong intervention.
10. Aschengrau A, Hardy S, Mackey P, et al. The impact of low technology lead hazard reduction activities among children with mildly elevated blood lead levels. Environ Res. 1998;79(1):41-50. doi: 10.1006/enrs.1998.3858. PMID: 9756679. Excluded: Wrong outcome.
11. Awasthi S, Awasthi R, Srivastav RC. Maternal blood lead level and outcomes of pregnancy in Lucknow, North India. Indian Pediatr. 2002;39(9):855-60. PMID: 12368533. Excluded: Wrong study design for Key Question.
12. Baghurst PA, Robertson EF, McMichael AJ, et al. The Port Pirie Cohort Study: lead effects on pregnancy outcome and early childhood development. Neurotoxicology. 1987;8(3):395-401. PMID: 2443882. Excluded: Wrong study design for Key Question.
13. Bajorek MM. Screening children for lead poisoning. West J Med. 1995;163(1):64. PMID: 7667984. Excluded: Not a study.
14. Baloh R, Sturm R, Green B, et al. Neuropsychological effects of chronic asymptomatic increased lead absorption. A controlled study. Arch Neurol. 1975;32(5):326-30. PMID: 1137507. Excluded: Wrong study design for Key Question.
15. Bartsocas CS, Grunt JA, Boylen GW, Jr., et al. Oral D-penicillamine and intramuscular BAL+EDTA in the treatment of lead accumulation. Acta Paediatr Scand. 1971;60(5):553-8. PMID: 4999890. Excluded: Wrong study design for Key Question.
16. Batagol R. Australian Drug Evaluation Committee: Medicines in pregnancy-An Australian categorisation of risk of drug use in pregnancy, 4th. Australian Government Publishing Service, Canberra, Australia; 1999. Excluded: Not a study.

Appendix A5. List of Excluded Studies

17. Beck RB, Rosenbaum,KN, Byers PH, et al. Ultrastructural findings in fetal penicillamine syndrome. Presentation and abstract, March of Dimes 14th Annual Birth Defects Conference, San Diego, CA; 1981. Excluded: Wrong outcome.

18. Bellinger D. Prenatal/early postnatal exposure to lead and risk of developmental impairment. Birth Defects Orig Artic Ser. 1989;25(6):73-97. PMID: 2481518. Excluded: Not a study.

19. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics. 1992;90(6):855-61. PMID: 1437425. Excluded: Wrong study design for Key Question.

20. Benson PF, Chisolm JJ, Jr. A reliable qualitative urine coproporphyrin test for lead intoxication in young children. J Pediatr. 1960;56:759-67. PMID: 13799015. Excluded: Wrong intervention.

21. Besunder JB, Super DM, Anderson RL. Comparison of dimercaptosuccinic acid and calcium disodium ethylenediaminetetraacetic acid versus dimercaptopropanol and ethylenediaminetetraacetic acid in children with lead poisoning. J Pediatr. 1997;130(6):966-71. PMID: 9202621. Excluded: Wrong comparator.

22. Bhattacharya A, Shukla R, Auyang ED, et al. Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead. Neurotoxicology. 2007;28(3):686-95. doi: 10.1016/j.neuro.2007.03.007. PMID: 17499360. Excluded: Wrong outcome.

23. Binns HJ, Kim D, Campbell C. Targeted screening for elevated blood lead levels: populations at high risk. Pediatrics. 2001;108(6):1364-6. PMID: 11731660. Excluded: Not a study.

24. Binns HJ, LeBailly SA, Fingar AR, et al. Evaluation of risk assessment questions used to target blood lead screening in Illinois. Pediatrics. 1999;103(1):100-6. PMID: 9917446. Excluded: Wrong comparator.

25. Binns HJ, LeBailly SA, Poncher J, et al. Is there lead in the suburbs? Risk assessment in Chicago suburban pediatric practices. Pediatric Practice Research Group. Pediatrics. 1994;93(2):164-71. PMID: 8121725. Excluded: Wrong comparator.

26. Blanksma LA, Sachs HK, Murray EF, et al. Failure of the urinary delta-aminolevulinic acid test to detect pediatric lead poisoning. Am J Clin Pathol. 1970;53(6):956-62. PMID: 5515391. Excluded: Wrong intervention.

27. Blumenthal S, Davidow B, Harris D, et al. A comparison between two diagnostic tests for lead poisoning. Am J Public Health. 1972;62(8):1060-4. PMID: 5046445. Excluded: Wrong intervention.

28. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol. 1999;150(6):590-7. PMID: 10489998. Excluded: Wrong study design for Key Question.

29. Bossarte RM, Brown MJ, Jones RL. Blood lead misclassification due to defective LeadCare blood lead testing equipment. Clin Chem. 2007;53(5):994-5. doi: 10.1373/clinchem.2006.082404. PMID: 17468412. Excluded: Not a study.

30. Bouhouch RR, El-Fadeli S, Andersson M, et al. Effects of wheat-flour biscuits fortified with iron and EDTA, alone and in combination, on blood lead concentration, iron status, and cognition in children: a double-blind randomized controlled trial. Am J Clin Nutr. 2016;104(5):1318-26. doi: 10.3945/ajcn.115.129346. PMID: 27733396. Excluded: Wrong intervention.

31. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. Clin Toxicol. 2009;47(7):617-31. doi: 10.1080/15563650903174828. PMID: 19663612. Excluded: Not a study.

32. Bradley JE, Baumgartner RJ. Subsequent mental development of children with lead encephalopathy, as related to type of treatment. J Pediatr. 1958;53(3):311-5. PMID: 13576382. Excluded: Wrong population.

Appendix A5. List of Excluded Studies

33. Braun JM, Hornung R, Chen A, et al. Effect of Residential Lead-Hazard Interventions on Childhood Blood Lead Concentrations and Neurobehavioral Outcomes: A Randomized Clinical Trial. JAMA Pediatr. 2018;172(10):934-42. doi: 10.1001/jamapediatrics.2018.2382. PMID: 30178064. Excluded: Wrong intervention.

34. Briss PA, Rosenblum LS. Screening strategies for lead poisoning. JAMA. 1993;270(21):2556; author reply -7. PMID: 8230637. Excluded: Not a study.

35. Bronson MA, Renier CM. The location of residence as a basis for childhood lead poisoning screening programs. Am J Public Health. 1995;85(4):589-90. PMID: 7702132. Excluded: Not a study.

36. Browder A, Joselow M, Foster J. Screening for detection of childhood lead poisoning in Newark. J Med Soc N J. 1974;71(1):45-8. PMID: 4520978. Excluded: Not a study.

37. Browder A, Joselow M, Louria DB, et al. Evaluation of screening programs for childhood lead poisoning by analysis of hospital admissions. Am J Public Health. 1974;64(9):914-5. PMID: 4425003. Excluded: Not a study.

38. Brown MJ, Meehan PJ. Health effects of blood lead levels lower than 10 mg/dl in children. Am J Public Health. 2004;94(1):8-9; author reply PMID: 14713682. Excluded: Not a study.

39. Brown SJ. Treatment and prevention of childhood lead poisoning: new approach. Wis Med J. 1973;72(8):175-7. PMID: 4199056. Excluded: Not a study.

40. Burke BL, Jr. Lead poisoning treatment. J Pediatr. 2006;149(3):428; author reply -9. doi: 10.1016/j.jpeds.2006.02.030. PMID: 16939771. Excluded: Not a study.

41. Burns MS, Shah LH, Marquez ER, et al. Efforts to identify at-risk children for blood lead screening in pediatric clinics--Clark County, Nevada. Clin Pediatr 2012;51(11):1048-55. doi: 10.1177/0009922812458352. PMID: 22935218. Excluded: Wrong outcome.

42. Byers RK, Maloof C. Edathamil calcium-disodium (versenate) in treatment of lead poisoning in children. AMA Am J Dis Child. 1954;87(5):559-69. PMID: 13157613. Excluded: Wrong study design for Key Question.

43. Campbell C, Gracely E, Tran M, et al. Primary prevention of lead exposure--blood lead results at age two years. Int J Environ Res Public Health. 2012;9(4):1216-26. doi: 10.3390/ijerph9041216. PMID: 22690192. Excluded: Wrong outcome.

44. Campbell C, Tran M, Gracely E, et al. Primary prevention of lead exposure: the Philadelphia lead safe homes study. Public Health Rep. 2011;126 Suppl 1:76-88. PMID: 21563715. Excluded: Wrong population.

45. Campbell JR, Schaffer SJ. Predicting the outcome of the CaNa2EDTA challenge test in children with moderately elevated blood lead levels. Environ Health Perspect. 1999;107(6):437-40. PMID: 10339443. Excluded: Wrong intervention.

46. Carpenter JW. Pediatric lead level screening. Alaska Med. 1993;35(2):173. PMID: 8238773. Excluded: Wrong study design for Key Question.

47. Casey R, Wiley C, Rutstein R, et al. Longitudinal assessment for lead poisoning. Clin Pediatr 1996;35(2):58-61. PMID: 8775476. Excluded: Wrong intervention.

48. Centers for Disease Control and Prevention. Blood lead levels among children in a managed-care organization--California, October 1992-March 1993. MMWR. 1995;44(34):627-9, 35. PMID: 7643848. Excluded: Wrong outcome.

49. Chen A, Rhoads GG, Cai B, et al. The effect of chelation on blood pressure in lead-exposed children: a randomized study. Environ Health Perspect. 2006;114(4):579-83. PMID: 16581549. Excluded: Wrong outcome.

50. Chen A, Schwarz D, Radcliffe J, et al. Maternal IQ, child IQ, behavior, and achievement in urban 5-7 year olds. Pediatr Res. 2006;59(3):471-7. doi: 10.1203/01.pdr.0000199910.16681.f0. PMID: 16492992. Excluded: Wrong study design for Key Question.

Appendix A5. List of Excluded Studies

51. Chisolm JJ, Jr. Chronic lead intoxication in children. Dev Med Child Neurol. 1965;7(5):529-36. PMID: 4956085. Excluded: Not a study.

52. Chisolm JJ, Jr. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J Pediatr. 1968;73(1):1-38. PMID: 4969284. Excluded: Not a study.

53. Chisolm JJ. Screening techniques for undue lead exposure in children: biological and practical considerations. J Pediatr. 1971;79(5):719-25. PMID: 4941955. Excluded: Not a study.

54. Chisolm JJ, Jr. Treatment of lead poisoning. Mod Treat. 1971;8(3):593-611. PMID: 5001054. Excluded: Not a study.

55. Chisolm JJ, Jr. Screening for lead poisoning in children. Pediatrics. 1973;51(2):280-3. PMID: 4695862. Excluded: Not a study.

56. Chisolm JJ, Jr. Management of increased lead absorption and lead poisoning in children. N Engl J Med. 1973;289(19):1016-8. doi: 10.1056/NEJM197311082891906. PMID: 4742201. Excluded: Not a study.

57. Chisolm JJ, Jr. Chelation therapy in children with subclinical plumbism. Pediatrics. 1974;53(3):441-3. PMID: 4205583. Excluded: Not a study.

58. Chisolm JJ, Jr. BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. J Toxicol Clin Toxicol. 1992;30(4):493-504. PMID: 1331490. Excluded: Not a study.

59. Chisolm JJ, Jr., Harrison HE. The treatment of acute lead encephalopathy in children. Pediatrics. 1957;19(1):2-20. PMID: 13400575. Excluded: Wrong population.

60. Chisolm JJ, Jr., Kaplan E. Lead poisoning in childhood--comprehensive management and prevention. J Pediatr. 1968;73(6):942-50. PMID: 4972778. Excluded: Not a study.

61. Chisolm JJ, Jr., Mellits ED, Keil JE, et al. A simple protoporphyrin assay-microhematocrit procedure as a screening technique for increased lead absorption in young children. J Pediatr. 1974;84(4):490-6. PMID: 4834244. Excluded: Wrong intervention.

62. Chisolm JJ, Jr., Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. J Pharmacol Exp Ther. 1985;235(3):665-9. PMID: 4078728. Excluded: Wrong comparator.

63. Chomchai C, Padungtod C, Chomchai S. Predictors of elevated blood lead level in Thai children: a pilot study using risk assessment questionnaire. J Med Assoc Thai. 2005;88 Suppl 8:S53-9. PMID: 16856427. Excluded: Wrong outcome.

64. Clark S, Grote J, Wilson J, et al. Occurrence and determinants of increases in blood lead levels in children shortly after lead hazard control activities. Environ Res. 2004;96(2):196-205. doi: 10.1016/j.envres.2003.11.006. PMID: 15325880. Excluded: Wrong comparator.

65. Clinical and Laboratory Standards Institute. Measurement procedures for the determination of lead concentrations in blood and urine. Second ed; 2013. Excluded: Not a study.

66. Coffin R, Phillips JL, Staples WI, et al. Treatment of lead encephalopathy in children. J Pediatr. 1966;69(2):198-206. PMID: 4957770. Excluded: Wrong population.

67. Cooke RE, Glynn KL, Ullmann WW, et al. Comparative study of a micro-scale test for lead in blood, for use in mass screening programs. Clin Chem. 1974;20(5):582-5. PMID: 4826953. Excluded: Wrong intervention.

68. Council on Environmental Health. Prevention of childhood lead toxicity. Pediatrics. 2016;138(1)doi: 10.1542/peds.2016-1493. Excluded: Not a study.

69. Counter SA, Ortega F, Shannon MW, et al. Succimer (meso-2,3-dimercaptosuccinic acid (DMSA)) treatment of Andean children with environmental lead exposure. Int J Occup Environ Health. 2003;9(2):164-8. doi: 10.1179/oeh.2003.9.2.164. PMID: 12848245. Excluded: Wrong population.

70. Creighton S, Hafner JW, Aldag JC. Effectiveness of a pediatric verbal lead exposure screening protocol in emergency department patients. Pediatr Emerg Care. 2013;29(2):156-61. doi: 10.1097/PEC.0b013e3182808abe. PMID: 23364376. Excluded: Wrong outcome.

71. Davis JR. Reliability of urinary delta-aminolevulinic acid as a mass screening technic for childhood exposure to lead. Am J Clin Pathol. 1970;53(6):967-9. PMID: 5509833. Excluded: Not a study.

72. De la Burde B, Choate MS, Jr. Does asymptomatic lead exposure in children have latent sequelae? J Pediatr. 1972;81(6):1088-91. PMID: 4643025. Excluded: Wrong study design for Key Question.

73. DeBaun MR, Sox HC, Jr. Setting the optimal erythrocyte protoporphyrin screening decision threshold for lead poisoning: a decision analytic approach. Pediatrics. 1991;88(1):121-31. PMID: 2057248. Excluded: Wrong intervention.

74. Delves HT. Blood collection for screening children for exposure to lead. Clin Chem. 1996;42(6 Pt 1):983-5. PMID: 8665698. Excluded: Not a study.

75. Dillard RA. Detection, evaluation, and management of children exposed to lead. Texas Med. 1978;74(11):65-8. PMID: 725776. Excluded: Not a study.

76. Donahue LA, Brennan GG. Lyophilized urea in Traverts solution for the treatment of lead encephalopathy. J Med Soc N J. 1962;59:456-9. PMID: 13887157. Excluded: Wrong population.

77. Dyal B. Are lead risk questionnaires adequate predictors of blood lead levels in children? Public Health Nurs. 2012;29(1):3-10. doi: 10.1111/j.1525-1446.2011.00961.x. PMID: 22211746. Excluded: Wrong comparator.

78. Edwards KS, Forsyth BW. Lead screening at pediatric teaching programs. Am J Dis Child. 1989;143(12):1455-7. PMID: 2589277. Excluded: Wrong outcome.

79. Esernio-Jenssen D, Bush V, Parsons PJ. Evaluation of VACUTAINER PLUS Low Lead tubes for blood lead and erythrocyte protoporphyrin testing. Clin Chem. 1999;45(1):148-50. PMID: 9895358. Excluded: Not a study.

80. Esteban E, Rubin CH, Jones RL, et al. Hair and blood as substrates for screening children for lead poisoning. Arch Environ Health. 1999;54(6):436-40. doi: 10.1080/00039899909603376. PMID: 10634234. Excluded: Wrong intervention.

81. 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. Int J Environ Res Public Health. 2015;12(12):15366-78. doi: 10.3390/ijerph121214989. PMID: 26633457. Excluded: Wrong outcome.

82. Ettinger AS, Lamadrid-Figueroa H, Mercado-Garcia A, et al. Effect of calcium supplementation on bone resorption in pregnancy and the early postpartum: a randomized controlled trial in Mexican women. Nutr J. 2014;13(1):116. doi: 10.1186/1475-2891-13-116. PMID: 25511814. Excluded: Wrong outcome.

83. Ettinger AS, Lamadrid-Figueroa H, Tellez-Rojo MM, et al. Effect of calcium supplementation on blood lead levels in pregnancy: a randomized placebo-controlled trial. Environ Health Perspect. 2009;117(1):26-31. doi: 10.1289/ehp.11868. PMID: 19165383. Excluded: Wrong population.

84. Farrar HC, McLeane LR, Wallace M, et al. A comparison of two dosing regimens of succimer in children with chronic lead poisoning. J Clin Pharmacol. 1999;39(2):180-3. PMID: 11563411. Excluded: Wrong comparator.

85. Fisher AA. Safety of ethylenediamine tetraacetate in the treatment of lead poisoning in persons sensitive to ethylenediamine hydrochloride. Cutis. 1991;48(2):105-6. PMID: 1935232. Excluded: Not a study.

86. Friedlander MA, Brooks CT, Sheehe PR. Blood pressure and creatinine clearance in lead-exposed children: the effect of treatment. Arch Environ Health. 1981;36(6):310-5. PMID: 7316569. Excluded: Wrong comparator.

87. Galke W, Clark S, Wilson J, et al. Evaluation of the HUD lead hazard control grant program: early overall findings. Environ Res. 2001;86(2):149-56. doi: 10.1006/enrs.2001.4259. PMID: 11437461. Excluded: Wrong comparator.

88. Gardella C. Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. Obstet Gynecol Surv. 2001;56(4):231-8. PMID: 11285436. Excluded: Not a study.

89. Garza A. Screening strategies for lead poisoning. JAMA. 1993;270(21):2555; author reply 6-7. PMID: 8230634. Excluded: Not a study.

90. Gause D, Chase W, Foster J, et al. Reduction in lead levels among children in Newark. J Med Soc N J. 1977;74(11):958-60. PMID: 269968. Excluded: Wrong study design for Key Question.

91. Gellert GA, Wagner GA, Maxwell RM, et al. Lead poisoning: from screening to primary prevention. Pediatrics. 1994;93(2):343-4. PMID: 8121754. Excluded: Not a study.

92. Gemmel DJ. Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. Obstet Gynecol. 1996;88(1):159-60. doi: 10.1016/0029-7844(96)88088-4. PMID: 8684754. Excluded: Not a study.

93. Ginot L, Fontaine A, Cheymol J, et al. [Evaluating the effectiveness of child lead poisoning prevention programs]. Rev Epidemiol Sante Publique. 2003;51(4):427-38. PMID: 13679735. Excluded: Not English language, but possibly relevant.

94. Glotzer DE, Weitzman M, Aschengrau A, et al. Economic evaluation of environmental interventions for low-level childhood lead poisoning. Ambulatory Child Health. 1997;3(3):255-67. Excluded: Wrong outcome.

95. Goldman LR. Lead screening. Pediatrics. 1993;91(4):854-5. PMID: 8464688. Excluded: Not a study.

96. Goodlad JK, Marcus DK, Fulton JJ. Lead and Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms: a meta-analysis. Clin Psychol Rev. 2013;33(3):417-25. doi: 10.1016/j.cpr.2013.01.009. PMID: 23419800. Excluded: Wrong intervention.

97. Graziano JH, Lolacono NJ, Meyer P. Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations. J Pediatr. 1988;113(4):751-7. PMID: 2845043. Excluded: Wrong comparator.

98. Graziano JH, Lolacono NJ, Moulton T, et al. Controlled study of meso-2,3-dimercaptosuccinic acid for the management of childhood lead intoxication. J Pediatr. 1992;120(1):133-9. PMID: 1309865. Excluded: Wrong comparator.

99. Groleau V, Herold RA, Schall JI, et al. Blood lead concentration is not altered by high-dose vitamin D supplementation in children and young adults with HIV. J Pediatr Gastroenterol Nutr. 2013;56(3):316-9. doi: 10.1097/MPG.0b013e3182758c4a. PMID: 23059649. Excluded: Wrong population.

100. Gutgesell ME. Lead screening in the general pediatric clinic. Va Med Q. 1996;123(3):190-1. PMID: 8752964. Excluded: Wrong comparator.

101. Hankin L, Hanson KR, Kornfeld JM, et al. Simplified method for mass screening for lead poisoning based on delta-aminolevulinic acid in urine. Clin Pediatr. 1970;9(12):707-12. PMID: 5487477. Excluded: Wrong intervention.

102. Hanna TL, Dietzler DN, Smith CH, et al. Erythrocyte porphyrin analysis in the detection of lead poisoning in children: evaluation of four micromethods. Clin Chem. 1976;22(2):161-8. PMID: 1248115. Excluded: Wrong intervention.

103. Haust HL, Ali H, Haines DS, et al. Short-term administration of dimercaptopropanol (BAL) and calcium disodium edetate (EDTA) for diagnostic and therapeutic lead mobilization. Int J Biochem. 1980;12(5-6):897-904. PMID: 6778726. Excluded: Wrong population.

Appendix A5. List of Excluded Studies

104. Heavey E. Lead poisoning: When an entire community is exposed. Nursing. 2016;46(9):28-33. doi: 10.1097/01.NURSE.0000490212.15944.5e. PMID: 27556165. Excluded: Not a study.

105. Hernandez-Avila M, Gonzalez-Cossio T, Hernandez-Avila JE, et al. Dietary calcium supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. Epidemiology. 2003;14(2):206-12. doi: 10.1097/01.Ede.0000038520.66094.34. PMID: 12606887. Excluded: Wrong population.

106. Hu H, Tellez-Rojo MM, Bellinger D, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect. 2006;114(11):1730-5. PMID: 17107860. Excluded: Wrong study design for Key Question.

107. Iniguez JL, Leverger G, Dollfus C, et al. Lead mobilization test in children with lead poisoning: validation of a 5-hour edetate calcium disodium provocation test. Arch Pediatr Adolesc Med. 1995;149(3):338-40. PMID: 7858698. Excluded: Wrong study design for Key Question.

108. Jacobziner H, Raybin HW. Lead poisoning treated with bal. N Y State J Med. 1964;64:441. PMID: 14118322. Excluded: Not a study.

109. Janakiraman V, Ettinger A, Mercado-Garcia A, et al. Calcium supplements and bone resorption in pregnancy: a randomized crossover trial. Am J Prev Med. 2003;24(3):260-4. PMID: 12657345. Excluded: Wrong outcome.

110. Jin Y, Yu F, Liao Y, et al. Therapeutic efficiency of succimer used with calcium and ascorbic acid in the treatment of mild lead-poisoning. Environ Toxicol Pharmacol. 2011;31(1):137-42. doi: 10.1016/j.etap.2010.09.015. PMID: 21787678. Excluded: Wrong comparator.

111. Jordan CM, Yust BL, Robison LL, et al. A randomized trial of education to prevent lead burden in children at high risk for lead exposure: efficacy as measured by blood lead monitoring. Environ Health Perspect. 2003;111(16):1947-51. PMID: 14644671. Excluded: Wrong intervention.

112. Kahn CA, Kelly PC, Walker WO, Jr. Lead screening in children with attention deficit hyperactivity disorder and developmental delay. Clin Pediatr. 1995;34(9):498-501. PMID: 7586924. Excluded: Wrong population.

113. Kalra V, Dua T, Kumar V, et al. Succimer in symptomatic lead poisoning. Indian Pediatr. 2002;39(6):580-5. PMID: 12084955. Excluded: Not a study.

114. Kaplowitz SA, Perlstadt H, D'Onofrio G, et al. The predictive value of self-report questions in a clinical decision rule for pediatric lead poisoning screening. Public Health Rep. 2012;127(4):375-82. PMID: 22753980. Excluded: Wrong study design for Key Question.

115. Kaplowitz SA, Perlstadt H, Perlstadt H, et al. Comparing lead poisoning risk assessment methods: census block group characteristics vs. zip codes as predictors. Public Health Rep. 2010;125(2):234-45. PMID: 20297750. Excluded: Wrong study design for Key Question.

116. Kassner J, Shannon M, Graef J. Role of forced diuresis on urinary lead excretion after the ethylenediaminetetraacetic acid mobilization test. J Pediatr. 1990;117(6):914-6. PMID: 2123241. Excluded: Wrong intervention.

117. Kaul B, Slavin G, Davidow B. Free erythrocyte protoporphyrin and zinc protoporphyrin measurements compared as primary screening methods for detection of lead poisoning. Clin Chem. 1983;29(8):1467-70. PMID: 6872205. Excluded: Wrong intervention.

118. Kawatu D, Weinberger HL, Blatt SD. Universal versus selective screening for lead in children. Pediatrics. 1995;95(1):157-9. PMID: 7770298. Excluded: Not a study.

119. Kegler MC, Malcoe LH. Results from a lay health advisor intervention to prevent lead poisoning among rural Native American children. Am J Public Health. 2004;94(10):1730-5. PMID: 15451742. Excluded: Wrong intervention.

Appendix A5. List of Excluded Studies

120. Kegler MC, Malcoe LH, Fedirko V. Primary prevention of lead poisoning in rural Native American children: behavioral outcomes from a community-based intervention in a former mining region. Fam Community Health. 2010;33(1):32-43. doi: 10.1097/FCH.0b013e3181c4e252. PMID: 20010003. Excluded: Wrong intervention.

121. Kimbrough RD, LeVois M, Webb DR. Management of children with slightly elevated blood lead levels. Pediatrics. 1994;93(2):188-91. PMID: 8121729. Excluded: Wrong study design for Key Question.

122. Knighton AJ, Payne NR, Speedie S. Lead Testing in a Pediatric Population: Underscreening and Problematic Repeated Tests. Journal of Public Health Management & Practice. 2016;22(4):331-7. doi: https://dx.doi.org/10.1097/PHH.0000000000000344. PMID: 26418307. Excluded: Wrong outcome.

123. Kornfeld JM, Ullmann WW, Hankin L. Modifications and use of the dipstick test, based on urinary delta-aminolevulinic acid (ALA), for the detection of lead poisoning in children. Clin Toxicol. 1972;5(1):7-16. doi: 10.3109/15563657208990503. PMID: 5043281. Excluded: Wrong intervention.

124. Kotok D. Development of children with elevated blood lead levels: a controlled study. J Pediatr. 1972;80(1):57-61. PMID: 5016353. Excluded: Wrong study design for Key Question.

125. Lanphear BP. The paradox of lead poisoning prevention. Science. 1998;281(5383):1617-8. PMID: 9767027. Excluded: Not a study.

126. Lanphear BP. Childhood lead poisoning prevention: too little, too late. JAMA. 2005;293(18):2274-6. doi: 10.1001/jama.293.18.2274. PMID: 15886384. Excluded: Not a study.

127. Liebelt EL, Shannon MW. Oral chelators for childhood lead poisoning. Pediatr Ann. 1994;23(11):616-9, 23-6. PMID: 7838614. Excluded: Not a study.

128. Lin-Fu JS. Screening for lead poisoning. Pediatrics. 1970;45(4):720-1. PMID: 5438184. Excluded: Not a study.

129. Lin-Fu JS. Diagnostic and screening procedures for lead poisoning. Pediatrics. 1971;48(3):488-9. PMID: 5094354. Excluded: Not a study.

130. Lioy PJ, Yiin LM, Adgate J, et al. The effectiveness of a home cleaning intervention strategy in reducing potential dust and lead exposures. J Expo Anal Environ Epidemiol. 1998;8(1):17-35. PMID: 9470102. Excluded: Wrong outcome.

131. Liu J, Gao D, Chen Y, et al. Lead exposure at each stage of pregnancy and neurobehavioral development of neonates. Neurotoxicology. 2014;44:1-7. doi: 10.1016/j.neuro.2014.03.003. PMID: 24704588. Excluded: Wrong study design for Key Question.

132. Lockitch G. Perspectives on lead toxicity. Clin Biochem. 1993;26(5):371-81. PMID: 8299207. Excluded: Not a study.

133. Mabry IR. Screening for elevated blood lead levels in children and pregnant women. Am Fam Phys. 2008;78(10):1201-2. PMID: 19035069. Excluded: Not a study.

134. Madlock YS, Bradley E. Childhood lead poisoning prevention program Memphis and Shelby County Health Department. Tenn Med. 2002;95(10):418-20. PMID: 12369542. Excluded: Not a study.

135. Mankikar D, Campbell C, Greenberg R. Evaluation of a home-based environmental and educational intervention to improve health in vulnerable households: Southeastern Pennsylvania lead and healthy homes program. Int J Environ Res Public Health. 2016;13(9):09. doi: 10.3390/ijerph13090900. PMID: 27618087. Excluded: Wrong intervention.

136. Marcus M, Hollander M, Lucas RE, et al. Micro-scale blood lead determinations in screening: evaluation of factors affecting results. Clin Chem. 1975;21(4):533-6. PMID: 1116287. Excluded: Wrong study design for Key Question.

137. Marcus SM. Treatment of lead-exposed children. Pediatrics. 1996;98(1):161-2; author reply 3. PMID: 8668396. Excluded: Not a study.

Appendix A5. List of Excluded Studies

138. Marcus SM, Joselow MM, Kemp F, et al. Warning: spurious elevations of blood lead in micro puncture techniques. J Pediatr. 1977;91(1):164. PMID: 874656. Excluded: Not a study.

139. Margulis HL. The control and prevention of pediatric lead poisoning in East Orange, New Jersey. J Environ Health. 1977;39(5):362-5. PMID: 10235755. Excluded: Not a study.

140. Markiewicz T. Recognizing, treating, and preventing lead poisoning. Am J Nurs. 1993;93(10):59-62, 4. PMID: 8213948. Excluded: Not a study.

141. Markowitz ME, Bijur PE, Ruff H, et al. Effects of calcium disodium versenate (CaNa2EDTA) chelation in moderate childhood lead poisoning. Pediatrics. 1993;92(2):265-71. PMID: 8337028. Excluded: Wrong study design for Key Question.

142. Mazur LJ, Moyer VA, Lally PA, et al. Evaluation of a lead screening program in Houston, Tex. Tex Med. 1996;92(1):54-7. PMID: 8599168. Excluded: Wrong outcome.

143. McCabe EB, Challop RS. Simple rapid test for lead poisoning. J Pediatr. 1972;80(5):893-4. PMID: 5018404. Excluded: Not a study.

144. McCloskey LJ, Bordash FR, Ubben KJ, et al. Decreasing the cutoff for elevated blood lead (EBL) can decrease the screening sensitivity for EBL. Am J Clin Pathol. 2013;139(3):360-7. doi: 10.1309/AJCP5RKWF3IZTCTO. PMID: 23429373. Excluded: Wrong study design for Key Question.

145. McKay CA, Jr. Role of chelation in the treatment of lead poisoning: discussion of the Treatment of Lead-Exposed Children Trial (TLC). J Med Toxicol. 2013;9(4):339-43. doi: 10.1007/s13181-013-0341-8. PMID: 24178899. Excluded: Not a study.

146. Miranda ML, Dolinoy DC, Overstreet MA. Mapping for prevention: GIS models for directing childhood lead poisoning prevention programs. Environmental Health Perspectives. 2002;110(9):947-53. PMID: 12204831. Excluded: Not a study.

147. Mitchell DG, Aldous KM, Ryan FJ. Mass screening for lead poisoning: Capillary blood sampling and automated Delves-cup atomic-absorption analysis. N Y State J Med. 1974;74(9):1599-603. PMID: 4527069. Excluded: Wrong intervention.

148. Montoya-Cabrera MA, Maldonado-Torres L, Velazwuez-Gutierrez L, et al. [Treatment of saturnism with a low dose of calcium disodium EDTA]. Arch Invest Med (Mex). 1974;5(3):603-8. PMID: 4218477. Excluded: Not English language, but possibly relevant.

149. Moriarty RW. Screening to prevent lead poisoning. Pediatrics. 1974;54(5):626-8. PMID: 4453465. Excluded: Not a study.

150. Ness R. Practice guidelines for childhood lead screening in primary care. J Pediatr Health Care. 2013;27(5):395-9. doi: 10.1016/j.pedhc.2012.12.013. PMID: 23465780. Excluded: Not a study.

151. Newton WP. Screening for lead poisoning in a suburban practice. J Fam Pract. 1995;41(1):95-6. PMID: 7798071. Excluded: Not a study.

152. Nicholson JS, Cleeton M. Validation and assessment of pediatric lead screener questions for primary prevention of lead exposure. Clin Pediatr. 2016;55(2):129-36. doi: 10.1177/0009922815584944. PMID: 25986443. Excluded: Wrong comparator.

153. Nordin JD, Rolnick SJ, Griffin JM. Prevalence of excess lead absorption and associated risk factors in children enrolled in a midwestern health maintenance organization. Pediatrics. 1994;93(2):172-7. PMID: 8121726. Excluded: Wrong comparator.

154. Nussbaumer-Streit B, Yeoh B, Griebler U, et al. Household interventions for preventing domestic lead exposure in children. Cochrane Database Syst Rev. 2016 (10). Excluded: Wrong intervention.

155. O'Donohoe NV. Lead poisoning in childhood treated by the subcutaneous administration of a chelating agent. Arch Dis Child. 1956;31(158):321-3. PMID: 13363476. Excluded: Not a study.

Appendix A5. List of Excluded Studies

156. Orava S, Brogan GX, Jr., Mofenson H, et al. Evaluation of two strategies for complying with state-mandated lead screening in the emergency department. Naussau-Suffolk Lead Committee, Naussau-Suffolk Lead Center. Acad Emerg Med. 1999;6(8):849-51. PMID: 10463559. Excluded: Wrong study design for Key Question.

157. Ossiander EM. A systematic review of screening questionnaires for childhood lead poisoning. J Public Health Manag Pract. 2013;19(1):E21-9. doi: 10.1097/PHH.0b013e3182249523. PMID: 22668673. Excluded: Systematic review or meta-analysis used as a source document only to identify individual studies.

158. Paulozzi LJ, Shapp J, Drawbaugh RE, et al. Prevalence of lead poisoning among two-year-old children in Vermont. Pediatrics. 1995;96(1 Pt 1):78-81. PMID: 7596728. Excluded: Wrong comparator.

159. Pawel MA, Frantz CN, Pisetsky IB. Screening for lead poisoning with the urinary ALA test. HSMHA Health Rep. 1971;86(11):1030-6. PMID: 5138281. Excluded: Wrong study design for Key Question.

160. Polivka BJ, Salsberry P, Casavant MJ, et al. Comparison of parental report of blood lead testing in children enrolled in Medicaid with Medicaid claims data and blood lead surveillance reports. J Community Health. 2006;31(1):43-55. PMID: 16482765. Excluded: Wrong intervention.

161. Prashant V, Prashant A, Devanand D, et al. Screening of school children for blood lead levels and attempts to reduce them by nonpharmacological means in a coastal city of India. Indian J Med Sci. 2008;62(5):185-92. PMID: 18579977. Excluded: Wrong population.

162. Pueschel SM, Kopito L, Schwachman H. Children with an increased lead burden. A screening and follow-up study. JAMA. 1972;222(4):462-6. PMID: 4677833. Excluded: Wrong study design for Key Question.

163. Rainey PM, Schonfeld DJ. Comparability of capillary and venous blood samples for lead screening. JAMA. 1994;272(19):1482. PMID: 7966831. Excluded: Not a study.

164. Ranmuthugala G, Karr M, Mira M, et al. Opportunistic sampling from early childhood centres: a substitute for random sampling to determine lead and iron status of pre-school children? Aust N Z J Public Health. 1998;22(4):512-4. PMID: 9659783. Excluded: Wrong comparator.

165. Rastogi S, Nandlike K, Fenster W. Elevated blood lead levels in pregnant women: identification of a high-risk population and interventions. J Perinat Med. 2007;35(6):492-6. doi: 10.1515/JPM.2007.131. PMID: 18052836. Excluded: Wrong study design for Key Question.

166. Raymond J, Wheeler W, Brown MJ, et al. Lead screening and prevalence of blood lead levels in children aged 1-2 years--Child Blood Lead Surveillance System, United States, 2002-2010 and National Health and Nutrition Examination Survey, United States, 1999-2010. MMWR Suppl. 2014;63(2):36-42. PMID: 25208256. Excluded: Wrong study design for Key Question.

167. Reuben A, Caspi A, Belsky D, et al. Association of childhood blood levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood. JAMA. 2017;317(12):1244-51. PMID: 28350927. Excluded: Wrong population.

168. Roberts JR, Hulsey TC, Curtis GB, et al. Using geographic information systems to assess risk for elevated blood lead levels in children. Public Health Rep. 2003;118(3):221-9. PMID: 12766217. Excluded: Wrong study design for Key Question.

169. Rolnick SJ, Nordin J, Cherney LM. A comparison of costs of universal versus targeted lead screening for young children. Environ Res. 1999;80(1):84-91. doi: 10.1006/enrs.1998.3879. PMID: 9931230. Excluded: Wrong comparator.

170. Rooney BL, Hayes EB, Allen BK, et al. Development of a screening tool for prediction of children at risk for lead exposure in a midwestern clinical setting. Pediatrics. 1994;93(2):183-7. PMID: 8121728. Excluded: Wrong comparator.

Appendix A5. List of Excluded Studies

171. Ruff HA, Bijur PE, Markowitz M, et al. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA. 1993;269(13):1641-6. PMID: 8455297. Excluded: Wrong outcome.

172. Sachs HK. Effect of a screening program on changing patterns of lead poisoning. Environ Health Perspect. 1974;7:41-5. PMID: 4831147. Excluded: Wrong study design for Key Question.

173. Sargent JD, Dalton M, Klein RZ. Diagnostic testing unwarranted for children with blood lead 10 to 14 microg/dL. Pediatrics. 1999;103(4):e51. PMID: 10103343. Excluded: Wrong study design for Key Question.

174. Sathyanarayana S, Beaudet N, Omri K, et al. Predicting children's blood lead levels from exposure to school drinking water in Seattle, Washington, USA. Ambul Pediatr. 2006;6(5):288-92. doi: 10.1016/j.ambp.2006.07.001. PMID: 17000419. Excluded: Wrong study design for Key Question.

175. Schaffer SJ, Szilagyi PG, Weitzman M. Lead poisoning risk determination in an urban population through the use of a standardized questionnaire. Pediatrics. 1994;93(2):159-63. PMID: 8121724. Excluded: Wrong comparator.

176. Schell LM, Denham M, Stark AD, et al. Relationship between blood lead concentration and dietary intakes of infants from 3 to 12 months of age. Environ Res. 2004;96(3):264-73. doi: 10.1016/j.envres.2004.02.008. PMID: 15364593. Exclusion: 2/

177. Schlenker TL, Baxmann R, McAvoy P, et al. Primary prevention of childhood lead poisoning through community outreach. WMJ. 2001;100(8):48-54. PMID: 12685297. Excluded: Wrong intervention.

178. Schlenker TL, Fritz CJ, Murphy A, et al. Feasibility and effectiveness of screening for childhood lead poisoning in private medical practice. Arch Pediatr Adolesc Med. 1994;148(7):761-4. PMID: 8019635. Excluded: Wrong outcome.

179. Schneider J, Aurori B, Armenti L, et al. Impact of community screening on diagnosis, treatment, and medical findings of lead poisoning in children. Public Health Rep. 1981;96(2):143-9. PMID: 7208798. Excluded: Wrong outcome.

180. Schonfeld DJ, Cullen MR, Rainey PM, et al. Screening for lead poisoning in an urban pediatric clinic using samples obtained by fingerstick. Pediatrics. 1994;94(2 Pt 1):174-9. PMID: 8036069. Excluded: Wrong study design for Key Question.

181. Schonfeld DJ, Rainey PM, Cullen MR, et al. Screening for lead poisoning by fingerstick in suburban pediatric practices. Arch Pediatr Adolesc Med. 1995;149(4):447-50. PMID: 7704175. Excluded: Wrong study design for Key Question.

182. Shannon MW, Townsend MK. Adverse effects of reduced-dose d-penicillamine in children with mild-to-moderate lead poisoning. Ann Pharmacother. 2000;34(1):15-8. PMID: 10669180. Excluded: Wrong comparator.

183. Shao L, Zhang L, Zhen Z. Interrupted time series analysis of children's blood lead levels: A case study of lead hazard control program in Syracuse, New York. PLoS ONE. 2017;12(2):e0171778. doi: 10.1371/journal.pone.0171778. PMID: 28182688. Excluded: Wrong study design for Key Question.

184. Sinclair DF, Dohnt BR. Sampling and analysis techniques used in a blood lead survey of 1241 children in Port Pirie, South Australia. Clin Chem. 1984;30(10):1616-9. PMID: 6478591. Excluded: Wrong intervention.

185. Smith HD. Lead poisoning in children and its therapy with EDTA. Ind Med Surg. 1959;28(3):148-51; discussion 51-5. PMID: 13630577. Excluded: Not a study.

186. Smith HD, King LR, Margolin EG. Treatment of lead encephalopathy. The combined use of edetate and hemodialysis. Am J Dis Child. 1965;109:322-4. PMID: 14261012. Excluded: Wrong population.

Appendix A5. List of Excluded Studies

187. Specter MJ, Guinee VF, Davidow B. The unsuitability of random urinary delta aminolevulinic acid samples as a screening test for lead poisoning. J Pediatr. 1971;79(5):799-804. PMID: 5116703. Excluded: Wrong outcome.

188. Stark AD, Quah RF, Meigs JW, et al. Relationship of sociodemographic factors to blood lead concentrations in New Haven children. J Epidemiol Community Health. 1982;36(2):133-9. PMID: 7119656. Excluded: Wrong study design for Key Question.

189. Stefanak MA, Bourguet CC, Benzies-Styka T. Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. Obstet Gynecol. 1996;87(2):209-12. doi: 10.1016/0029-7844(95)00397-5. PMID: 8559525. Excluded: Wrong population.

190. Striph KB. Prevalence of lead poisoning in a suburban practice. J Fam Pract. 1995;41(1):65-71. PMID: 7798067. Excluded: Wrong comparator.

191. Swindell SL, Charney E, Brown MJ, et al. Home abatement and blood lead changes in children with class III lead poisoning. Clin Pediatr (Phila). 1994;33(9):536-41. doi: 10.1177/000992289403300905. PMID: 8001322. Excluded: Wrong comparator.

192. Thurtle N, Greig J, Cooney L, et al. Description of 3,180 courses of chelation with dimercaptosuccinic acid in children < 5 y with severe lead poisoning in Zamfara, Northern Nigeria: a retrospective analysis of programme data. PLoS Medicine. 2014;11(10):e1001739. doi: 10.1371/journal.pmed.1001739. PMID: 25291378. Excluded: Wrong population.

193. Tressou J, Crepet A, Bertail P, et al. Probabilistic exposure assessment to food chemicals based on extreme value theory. Application to heavy metals from fish and sea products. Food Chem Toxicol. 2004;42(8):1349-58. doi: 10.1016/j.fct.2004.03.016. PMID: 15207386. Excluded: Wrong study design for Key Question.

194. Triantafyllidou S, Gallagher D, Edwards M. Assessing risk with increasingly stringent public health goals: the case of water lead and blood lead in children. J Water Health. 2014;12(1):57-68. doi: 10.2166/wh.2013.067. PMID: 24642433. Excluded: Wrong study design for Key Question.

195. Triantafyllidou S, Le T, Gallagher D, et al. Reduced risk estimations after remediation of lead (Pb) in drinking water at two US school districts. Sci Total Environ. 2014;466-467:1011-21. doi: 10.1016/j.scitotenv.2013.07.111. PMID: 23988746. Excluded: Wrong outcome.

196. Verebey K. Filter paper-collected blood lead testing in children. Clin Chem. 2000;46(7):1024-8. PMID: 10894859. Excluded: Not a study.

197. Verebey K, Rosen JF, Schonfeld DJ, et al. Blood collection and analytical considerations in blood lead screening in children. Clin Chem. 1995;41(3):469-70. PMID: 7882527. Excluded: Not a study.

198. Veyhe AS, Hofoss D, Hansen S, et al. The Northern Norway Mother-and-Child Contaminant Cohort (MISA) Study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy. Int J Hyg Environ Health. 2015;218(2):254-64. doi: 10.1016/j.ijheh.2014.12.001. PMID: 25556042. Excluded: Wrong study design for Key Question.

199. Vitale LF, Rosalinas-Bailon A, Folland D, et al. Oral penicillamine therapy for chronic lead poisoning in children. J Pediatr. 1973;83(6):1041-5. PMID: 4757518. Excluded: Wrong comparator.

200. Wang ST, Pizzolato S, Peter F. Microsampling technique and determination of blood lead by Zeeman atomic absorption spectrophotometry. Sci Total Environ. 1988;71(1):37-43. PMID: 3358115. Excluded: Wrong outcome.

201. Wasserman LR. The effects of a family-based educational intervention on the prevention of lead poisoning in children (EdD). 2002. Excluded: Wrong study design for Key Question.

Appendix A5. List of Excluded Studies

202. Watt GC, Britton A, Gilmour WH, et al. Is lead in tap water still a public health problem? An observational study in Glasgow. BMJ. 1996;313(7063):979-81. PMID: 8892418. Excluded: Wrong study design for Key Question.

203. Wei Z, Markowitz M, clement I. Therapeutic effectiveness of calcium supplementation on moderate lead poisoning in children: a double-blind randomized clinical trial. Zhonghua Er Ke Za Zhi. 1998;36(3):146-8. Excluded: Not English language, but possibly relevant.

204. Willis FR, Rossi E, Bulsara M, et al. The Fremantle lead study. J Paediatr Child Health. 1995;31(4):326-31. PMID: 7576892. Excluded: Wrong study design for Key Question.

205. Yiin LM, Lioy PJ, Rhoads GG. Impact of home carpets on childhood lead intervention study. Environ Res. 2003;92(2):161-5. PMID: 12854696. Excluded: Wrong comparator.

206. Zabel EW, Falken MC, Sonnabend M, et al. Prevalence of elevated blood lead levels and evaluation of a lead-risk-screening questionnaire in rural Minnesota. J Environ Health. 2005;68(2):9-15, 36. PMID: 16220717. Excluded: Wrong comparator.

207. Zheng J, Huynh T, Gasparon M, et al. Human health risk assessment of lead from mining activities at semi-arid locations in the context of total lead exposure. Environ Sci Pollut Res Int. 2013;20(12):8404-16. doi: 10.1007/s11356-013-2145-4. PMID: 24122159. Excluded: Wrong study design for Key Question.

208. Zierold KM, Havlena J, Anderson H. Exposure to lead and length of time needed to make homes lead-safe for young children. Am J Public Health. 2007;97(2):267-70. doi: 10.2105/AJPH.2005.067603. PMID: 17194869. Excluded: Wrong outcome.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on above criteria:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables
Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than
80 percent or attention to some but not all important confounding variables
Poor: Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies
Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients
Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers

screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

*Reference: U.S. Preventive Services Task Force Procedure Manual. July 2017. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A7. Expert Reviewers of the Draft Report

- Jennifer A. Lowry, MD, Chief, Section of Toxicology and Environmental Health, Children's Mercy
- Suril Mehta, MPH, Health Scientist, Office of the Report on Carcinogens, U.S. National Toxicology Program, National Institute of Environmental Health Sciences
- Matthew Strickland, PhD, MPH, Associate Professor of Epidemiology, School of University Health Sciences, University of Nevada, Reno
- Federal Partners from the United States Environmental Protection Agency
  - Ruth A. Etzel, MD, PhD, Director, Office of Children's Health Protection, United States Environmental Protection Agency
- Additional Federal Partners from the Centers for Disease Control and Prevention
  - Brandy Peaker, MD, MPH, CDC Liason, Centers for Disease Control and Prevention

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Screening test	Definition of a positive screening exam	Reference standard	Type of study	Country Setting	Population characteristics	Sample size Proportion with condition
Casey, 1994[43]	CDC Risk Assessment Questionnaire	≥1 positive answers	Venous	Cross-sectional	United States Urban general pediatric department	Low-risk vs. high-risk Mean age, months: 10 vs. 9 Female: 50% vs. 50% Ethnicity: 29% vs. 33% African American 62% vs. 62% white	n=167 Elevated BLL, overall ≥10 µg/dL: 29% (48/165) 10 to 14 µg/dL: 22% (36/165) 15 to 19 µg/dL: 4% (7/165) 20 to 44 µg/dL: 2.5% (4/165) 46 µg/dL: 0.5% (1/165)
Dalton, 1996[44]	CDC Risk Assessment Questionnaire Additional behavioral risk factor questions	≥1 positive or equivocal answers	Venous	Cross-sectional	United States Medical center	Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR	n=516 Elevated BLL, overall ≥10 µg/dL: 22% (101/463) ≥15 µg/dL: 6% (28/463)
France, 1996[48]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answers	Venous	Cross-sectional	United States Multisite primary care network	Mean age: NR (range, 5 months to 6.5 years) Female: NR Ethnicity: NR	n=2,978 Mean BLL: 4.19 µg/dL Elevated BLL ≥10 µg/dL: 2.9% (85/2978)
Holmes, 1997[49]	CDC Risk Assessment Questionnaire Additional risk factor questions	Unclear	Venous	Cross-sectional	United States Continuity clinic at a children's hospital	Mean age, months: 28.44 (range, 9 to 72) Female: 46% Ethnicity: 39% Hispanic, 39% black, 18% white	n=754 Elevated BLL ≥10 µg/dL: 3.1% (25/801)

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Proportion unexaminable by screening test	Analysis of screening failures	Proportion who underwent reference standard and included in analysis	Sensitivity (95% CI)	Specificity (95% CI)
Casey, 1994[43]	n=2	NR	98% (165/167)	Overall: 40% (19/48) (25.77 to 54.73) By screening question: Peeling paint: 15% Renovation: 31% Sibling with Pb: 6% Adult's job with Pb: 2% Live near Pb industry: 6%	Overall: 60% (70/117) (50.36 to 68.78) By screening question: Peeling paint: 76% Renovation: 75% Sibling with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%
Dalton, 1996[44]	n=0	NR	89.7% (463/516)	CDC Risk Factors Overall: 70.3% (60.39 to 78.98) Behavioral Risk Factors Playing near outside of house: 74.2% (64.60 to 82.44)	CDC Risk Factors Overall: 31.8% (27.00 to 36.84) Behavioral Risk Factors Playing near outside of house: 54.1% (28.05 to 37.98)
France, 1996[48]	n=562 (19%)	Prevalence of elevated BLL did not differ for those who did not complete screening questionnaire: 3.2% (p=0.51)	81% (2,416/2,978)	CDC + additional questions: 59.7% (48 to 72) CDC alone: 57% (45 to 69)	CDC + additional questions: 36% (34 to 38) CDC alone: 51% (49 to 53)
Holmes, 1997[49]	n=47 (5.9%)	NR	94% (754/801)	68% (46.50 to 85.05)	58% (53.93 to 61.23)

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality rating
Casey, 1994[43]	Overall: 1.0 (0.65 to 1.49) Peeling paint: 0.625 Renovation: 1.24 Sibling with Pb: 6.0 Adult's job: 0.67 Live near Pb: 3	Overall: 1.0 (0.77 to 1.33) Peeling paint: 1.12 Renovation: 0.92 Sibling with Pb: 0.95 Adult's job: 1.01 Live near Pb: 0.96	Overall: 29% (19/66) (21.09 to 37.94) Peeling paint: 20% Renovation: 34% Sibling with Pb: 75% Adult's job: 25% Live near Pb: 60%	Overall: 71% (76/99) (64.75 to 76.03) Peeling paint: 68% Renovation: 73% Sibling with Pb: 72% Adult's job: 71% Live near Pb: 72%	Fair
Dalton, 1996[44]	CDC risk factors: 1.03 (0.89 to 1.19) Playing near outside of house: 1.62 (0.97 to 1.27)	CDC risk factors: 0.93 (0.67 to 1.31) Playing near outside of house: 0.78 (0.54 to 1.13)	CDC risk factors: 22.33% (19.91 to 24.94) Playing near outside of house: 23.58% (21.23 to 26.12)	CDC risk factors: 79.31% (73.26 to 84.29) Playing near outside of house: 82.07% (76.11 to 86.80)	Fair
France, 1996[48]	CDC + additional questions: 0.93 (NR) CDC alone: 1.16 (NR)	CDC + additional questions: 1.12 (NR) CDC alone: 0.84 (NR)	CDC + additional questions: 2.8 (NR) CDC alone: NR	CDC + additional questions: NR CDC alone: NR	Fair
Holmes, 1997[49]	1.60 (1.21 to 2.13)	0.56 (0.31 to 0.99)	5.21% (3.98 to 6.80)	98.13% (96.73 to 98.94)	Fair

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Screening test	Definition of a positive screening exam	Reference standard	Type of study	Country Setting	Population characteristics	Sample size Proportion with condition
Kazal, 1997[47]	CDC Risk Assessment Questionnaire Additional risk factor questions	Unclear	Venous	Cross-sectional	United States Rural clinic, Navajo Reservation	Mean age, months: 30.5 Female: 49% Ethnicity: 98% Navajo	n=368 Elevated BLL ≥10µg/dL: 2.2% (8/368)
Muniz, 2003[50]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answers	Venous	Retrospective cohort	United States Rural clinic	Mean age: NR (range, 9 to 24 months) Female: NR Ethnicity: NR	n=171 Elevated BLL ≥10 µg/dL: 2.3% (4/171)
Robin, 1997[45]	Modified Health Care Financing Administration questionnaire	≥1 positive answers	Venous	Cross-sectional	United States Urban and rural Medicaid recipients	Mean age: NR (range, 2 to 6 years) Female: 51.3% Ethnicity: Alaska native: 60% White: 28% Black: 5%	n=967 Elevated BLL ≥10 µg/dL: 0.6% (6/967)
Schaffer, 1996[51]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answers to the CDC questions	Venous (approximately 6% were capillary)	Cross-sectional	United States Rural clinic	Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR	n=705 Elevated BLL ≥10 µg/dL: 8.4% (59/705)
Snyder, 1995[46]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive answers	Venous	Cross-sectional	United States Public clinics	Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR	n=247 Elevated BLL ≥10 µg/dL: 7.7% (19/247)

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Proportion unexaminable by screening test	Analysis of screening failures	Proportion who underwent reference standard and included in analysis	Sensitivity (95% CI)	Specificity (95% CI)
Kazal, 1997[47]	n=45 (12.2%)	NR	100%	CDC questions: 42.9% (9.90 to 81.59) CDC + additional questions: 42.9% (NR)	CDC questions: 68.52% (68.52 to 78.50) CDC + additional questions: 66.1% (NR)
Muniz, 2003[50]	n=0	NR	100%	CDC questions: 25% (NR) CDC + additional questions: 50.0% (6.76 to 93.24)	CDC questions: 49% (NR) CDC + additional questions: 49.70 (41.88 to 57.53)
Robin, 1997[45]	n=0	NR	100%	83.3% (35.88 to 99.58)	38.6% (35.50 to 41.77)
Schaffer, 1996[51]	n=1 (0.1%)	NR	99.2% (705/711)	CDC + additional questions: 75% (NR) Condensed questionnaire from 4 items most likely to correctly identify patients: 88% (NR)	CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR
Snyder, 1995[46]	n=0	NR	100%	CDC questions: 31.6% (12.58 to 56.55) Additional questions: 89.5% (66.86 to 98.70) CDC + additional questions: 89.5% (66.6 to 98.70)	CDC questions: 79.8 (74.02 to 84.83) Additional questions: 37.3% (30.99 to 43.91) CDC + additional questions: 31.6% (25.6 to 38.0)

Appendix B1. Data Abstraction of Screening Questionnaire Studies

Study, year	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality rating
Kazal, 1997[47]	1.63 (0.68 to 3.91) CDC + additional questions: 1.27 (NR)	0.77 (0.41 to 1.48) CDC + additional questions: 0.79 (NR)	3.49% (1.48 to 7.98) CDC + additional questions: 2.7 (NR)	98.31% (96.83 to 99.11) CDC + additional questions: 98.1 (NR)	Fair
Muniz, 2003[50]	CDC + additional questions: 0.99 (0.37 to 2.68)	CDC + additional questions: 1.01 (0.37 to 2.71)	CDC + additional questions: 2.33% (0.88 to 6.03)	CDC + additional questions: 97.65% (93.90 to 99.11)	Fair
Robin, 1997[45]	1.36 (0.95 to 1.95)	0.43 (0.07 to 2.59)	0.84% (0.59 to 1.21)	99.73% (98.40 to 99.95)	Fair
Schaffer, 1996[51]	CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR	CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR	CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR	CDC + additional questions: 98% Condensed questionnaire from 4 items most likely to correctly identify patients: 98% (NR)	Fair
Snyder, 1995[46]	CDC questions: 1.57 (0.77 to 3.19) Additional questions: 1.43 (1.19 to 1.71) CDC + additional questions: 1.31 (1.09 to 1.56)	CDC questions: 0.86 (0.63 to 1.17) Additional questions: 0.28 (0.08 to 1.06) CDC + additional questions: 0.33 (0.09 to 1.25)	CDC questions: 11.54% (6.02 to 20.98) Additional questions: 10.6% (9.00 to 12.5) CDC + additional questions: 9.83% (8.36 to 11.52)	CDC questions: 93.33% (91.11 to 95.03) Additional questions: 97.7% (91.89 to 99.38) CDC + additional questions: 97.3 (90.54 to 99.27)	Fair

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; LR=likelihood ratio; NR=not reported; Pb=lead.

Appendix B2. Data Abstraction of Capillary Screening Studies

Study, year	Screening test	Definition of a positive screening exam	Reference standard	Type of study	Country Setting	Population Characteristics	Sample size Proportion with condition	Proportion unexaminable by screening test
Holtrop, 1998[61]	Capillary	≥10 µg/dL ≥15 µg/dL ≥20 µg/dL	Venous	Prospective cohort	United States Urban clinic	Mean age: NR Female sex: 41% Ethnicity: 97% black	n=124 Elevated BLL, ≥10 µg/dL: 26% (31/120)	0%
Parsons, 1997[27]	Capillary	≥10 µg/dL ≥15 µg/dL ≥20 µg/dL ≥25 µg/dL	Venous	Prospective cohort	United States County health clinics and university hospital	Mean age: NR (range, 0 to 12 years) Female sex: 43% Ethnicity: 38% white, 28% black, 21% Hispanic, 6% Asian	n=499 Elevated BLL ≥10 µg/dL: 30.5% Elevated BLL ≥15 µg/dL: 16.7% Elevated BLL ≥20 µg/dL: 9.9% Elevated BLL ≥25 µg/dL: 6.6%	5% (29/533)
Sargent, 1996[62] See also: Sargent, 1996[83]	Capillary	≥8 µg/dL ≥10 µg/dL ≥12 µg/dL ≥15 µg/dL	Venous	Prospective cohort	United States Urban clinic	NR	n=513 Elevated BLL ≥10 µg/dL: 20.5% Elevated BLL ≥20 µg/dL: 2.3%	2.7% (16/586)
Schlenker, 1994[63]	Capillary Method 1: alcohol wipe Method 2: alcohol + silicone Method 3: soap and water + alcohol Method 4: soap and water, alcohol, and 1% nitric acid solution	≥20 µg/dL	Venous	Prospective cohort	United States Urban health department and clinics	Mean age: 3 years Female sex: 47% Ethnicity: 88% black	n=295 Elevated BLL: NR	NR

Appendix B2. Data Abstraction of Capillary Screening Studies

Study, year	Proportion who underwent reference standard and included in analysis	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality rating
Holtrop, 1998[61]	97% (120/124)	≥10 µg/dL: 94% (NR) ≥15 µg/dL: 75% (NR) ≥20 µg/dL: 78% (NR)	≥10 µg/dL: 99% (NR) ≥15 µg/dL: 98% (NR) ≥20 µg/dL: 100% (NR)	≥10 µg/dL: 94 ≥15 µg/dL: 37.5 ≥20 µg/dL: Not estimable	≥10 µg/dL: 0.06 ≥15 µg/dL: 0.26 ≥20 µg/dL: 0.22	≥10 µg/dL: 97% (NR) ≥15 µg/dL: 86% (NR) ≥20 µg/dL: 100% (NR)	≥10 µg/dL: 98% (NR) ≥15 µg/dL: 96% (NR) ≥20 µg/dL: 98% (NR)	Poor
Parsons, 1997[27]	93.6% (499/533)	≥10 µg/dL: 87.5% (81.8 to 91.9) ≥15 µg/dL: 83.0% (74.8 to 89.5) ≥20 µg/dL: 81.8% (70.4 to 90.2) ≥25 µg/dL: 82.5% (67.2 to 92.3)	≥10 µg/dL: 93.2% (90.0 to 95.6) ≥15 µg/dL: 95.3% (92.8 to 97.2) ≥20 µg/dL: 97.3% (95.3 to 98.6) ≥25 µg/dL: 98.5% (96.9 to 99.4)	≥10 µg/dL: 12.9 (8.6 to 19.2) ≥15 µg/dL: 17.7 (11.4 to 27.7) ≥20 µg/dL: 30.3 (17.2 to 53.6) ≥25 µg/dL: 54.8 (25.9 to 115.9)	≥10 µg/dL: 0.13 (0.09 to 0.20) ≥15 µg/dL: 0.18 (0.12 to 0.27) ≥20 µg/dL: 0.19 (0.11 to 0.31) ≥25 µg/dL: 0.18 (0.09 to 0.35)	≥10 µg/dL: 87.5% (82.5 to 91.3) ≥15 µg/dL: 83.0% (75.8 to 88.4) ≥20 µg/dL: 81.8% (71.8 to 88.8) ≥25 µg/dL: 82.5% (69.0 to 90.9)	≥10 µg/dL: 93.2% (90.3 to 95.3) ≥15 µg/dL: 95.3% (93.1 to 96.9) ≥20 µg/dL: 97.3% (95.6 to 98.4) ≥25 µg/dL: 98.5% (97.1 to 99.2)	Fair
Sargent, 1996[62] See also: Sargent, 1996[83]	88% (513/586)	≥8 µg/dL: 100% (NR) ≥10 µg/dL: 91% (NR) ≥12 µg/dL: 63% (NR)	≥8 µg/dL: NR ≥10 µg/dL: 92.2% (NR) ≥12 µg/dL: NR ≥15 µg/dL: NR	NR	NR	≥8 µg/dL: NR ≥10 µg/dL: 74.8% (NR) ≥12 µg/dL: NR ≥15 µg/dL: NR	NR	Fair
Schlenker, 1994[63]	100%	Method 1: 95% (NR) Method 2: 96% (NR) Method 3: 88% (NR) Method 4: 86% (NR)	Method 1: 94% (NR) Method 2: 96% (NR) Method 3: 100% (NR) Method 4: 91% (NR)	Method 1: 15.8 Method 2: 24.0 Method 3: Not estimable Method 4: 9.6	Method 1: 0.05 Method 2: 0.04 Method 3: 0.12 Method 4: 0.15	NR	NR	Poor

Abbreviations: BLL=blood lead level; CI=confidence interval; NR=not reported.

Appendix B3. Data Abstraction of Childhood Treatment Trials

Author, year	Study design	Setting Country	Study duration Mean followup	Interventions (N)	Inclusion criteria	Patient characteristics	Loss to followup	Adjusted variables for statistical analysis (for observational studies)
Boreland, 2009[69]	RCT	Lead-mining neighborhood Australia	Duration: mean 13 months	A. Immediate lead home remediation (n=45) B. Delayed lead home remediation (n=45)	Children ages 12 to 60 months with BLL 15 to 29 µg/dL	Age: 3.5 years Race: NR Sex: 58% female BLL: 15 to 19 µg/dL: 28% BLL: 20 to 24 µg/dL: 23% BLL: 25 to 29 µg/dL: 37% BLL: >30 µg/dL: 12%	Loss to followup: 2% (1/45) vs. 2% (1/45)	Sex, location, lead loading, lead paint, dust proofing, soil lead, yard dust potential, general environment, and age at remediation
Brown, 2006[70]	RCT	Rhode Island Department of Health United States	Duration: 1 year	A. 5 home visits from a nurse (n=92) B. Usual care, including educational outreach about lead poisoning (n=83)	Children age <28 months with BLL 15 to 19 µg/dL	A vs. B Age: 19.1 vs. 18.8 months Race: 47% white, 40% Hispanic, 8% black vs. 39% white, 49% Hispanic, 10% black Sex: NR BLL: 16.5 vs. 16.6 µg/dL	Loss to followup: 13% (22/175)	NR
Nicholson, 2017[73]	RCT	Urban children's hospital United States	Duration: 6 months	A. Professional lead inspection and cleaning kit B. Professional lead inspection C. Cleaning kit D. EPA lead exposure pamphlets	Low income families with children age <6 years and BLL 3 to 9.9 µg/dL	Age: 3.94 years Race: NR Sex: NR BLL, µg/dL (A vs. B vs. C vs. D): 5.18 vs. 5.75 vs. 5.25 vs. 5.02	Loss to followup: 8.3%	NR
O'Connor, 1999[68]	RCT	Urban children's hospital United States	Duration: 6 months	E. DMSA chelation 100 to 200 mg 3 times daily (dose weight-dependent) (n=19) F. Placebo (n=20)	Children ages 2.5 to 5 years with BLL 30 to 45 µg/dL	A vs. B Age: 39.8 vs. 40.8 months Race: NR Sex: 68% vs. 35% female Mean BLL: 34.9 vs. 33.0 µg/dL	Loss to followup: 5% (2/39)	NR
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[64] See also: Rogan, 2001[67]; Liu, 2002[66]; Dietrich, 2004[65]	RCT	Multiple urban clinics United States	Duration: 3 years	A. Succimer, dose dependent on body surface area (n=396) B. Placebo (n=384)	Children ages 12 to 33 months with BLL 20 to 44 µg/dL	A vs. B Age: 24 vs. 24 months Race: 78% black, 12% white, 6% Hispanic, 4% other vs. 76% black, 11% white, 7% Hispanic, 6% other Sex: 45% vs. 43% female BLL: 26 vs. 26 µg/dL	Loss to followup: 17% (69/396) vs. 15% (59/384)	NR

Appendix B3. Data Abstraction of Childhood Treatment Trials

Author, year	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality rating	Funding source
Boreland, 2009[69]	BLL: 17.5 vs. 17.9 µg/dL; mean change, 1% (95% CI, -11 to 11)	NR	NR	Fair	Australian Department of Health and Ageing
Brown, 2006[70]	BLL did not differ between groups at 3, 6, or 12 months (data only reported in a figure) Last available BLL test >10 µg/dL: 51% vs. 51%; p=NS Any BLL test >20 µg/dL: 8% vs. 11%; p=NS	NR	NR	Fair	Maternal and Child Health Bureau of the Centers for Disease Control and Prevention
Nicholson, 2017[73]	Change in BLL at 6 months: -2.54 vs. -2.99 vs. -2.46 vs. -2.26, no significant differences	NR	NR	Fair	Grant funding
O'Connor, 1999[68]	1 month BLL, mean: 27.4 vs. 33.2 µg/dL; p=NS 6 months BLL, mean: 28.8 vs. 25.1 µg/dL; p=NS	NR	NR	Fair	Case Western University
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[64] See also: Rogan, 2001[67]; Liu, 2002[66]; Dietrich, 2004[65]	6 months BLL: mean difference, -4.5 µg/dL (95% CI, -3.7 to -5.3) 12 months BLL: mean difference, -2.7 µg/dL (95% CI, -1.9 to -3.5) Age 7 years BLL >10 µg/dL: 25% vs. 27%; p=NS	36 months No differences in WPPSI-R, NEPSY, or CPRS neurodevelopment scales or any of their subscales[67] No difference or change in WPPSI-R or Bayley Scale of Infant Development cognitive scale scores[66] No differences in WISC-III, NEPSY, or WLPB-R cognition scales; BASC behavior scales; CVLT-C learning and memory scales; CPT attention scale; or CPT or NESS neuromotor scales[65]	3 months Hospitalizations: 5.6% vs. 3.9%; p=NS No differences in rates of any adverse event 36 months No difference between groups in any category of adverse events (data not reported in paper but available online)[66] Height at age 7 years shorter in succimer-treated patients by 1.17 cm (95% CI, 0.41 to 1.93)	Good	National Institute of Environmental Health Sciences, National Institutes of Health, and Centers for Disease Control and Prevention

Abbreviations: BASC=Behavior Assessment System for Children; BLL=blood lead level; CI=confidence interval; CPRS=Conners' Parent Rating Scale; CPT=Conners' Continuous Performance Test; CVLT-C=California Verbal Learning Test-Children's Version; NEPSY=a developmental neuropsychological assessment neuropsychological test; NESS=Neurological Examination for Soft Signs; NR=not reported; NS=not significant; RCT=randomized, controlled trial; WISC-III=Wechsler Intelligence Scale for Children-3rd edition; WLPB-R=Woodcock Language Proficiency Battery-Revised; WPPSI-R= Wechsler Preschool and Primary Scale of Intelligence-Revised.

Appendix C1. Quality Assessment of Childhood Diagnostic Accuracy Studies

Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index text?	Was there an appropriate interval between index test and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality rating
Casey, 1994[43]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Fair
Dalton, 1996[44]	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	No	Fair
France, 1996[48]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Holmes, 1997[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Fair
Holtrop, 1998[61]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Kazal, 1997[47]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Muniz, 2003[50]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Yes	Yes	Fair
Parsons, 1997[27]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Robin, 1997[45]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sargent, 1996[62]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Schaffer, 1996[51]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	No	No	No	Fair
Schlenker, 1994[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Snyder, 1995[46]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Fair
Tejeda, 1994[60]	No	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Poor

Appendix C2. Quality Assessment of Childhood Trials

Author,year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup differential/ high?	Analyze people in the groups in which they were randomized?	Quality rating
Boreland, 2009[69]	Unclear	Unclear	Yes; matched	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
Brown, 2006[70]	Yes	Yes	Yes	Yes	Yes	No; not for the intervention group	No	Yes	No/No	Yes	Fair
Markowitz, 2004[71]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes (34% overall)	Yes	Poor
Nicholson, 2017[73]	No (shuffled envelopes)	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
O'Connor, 1999[68]	Unclear	Unclear	No; not sex	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Fair
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[64] See also: Rogan, 2001[67]; Liu, 2002[66]; Dietrich, 2004[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Wolf, 2003[72]	Unclear	Unclear	Unclear; only BLL reported	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Poor

Abbreviation: BLL=blood lead level.

Appendix C3. Quality Assessment of Childhood Cohort Studies

Author, year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article maintain comparable groups (report attrition, contamination, adherence, and cross-over)?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential or overall high loss to followup?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Shannon, 1988[74]	Yes; all	Unclear	Unclear	Unclear	Unclear	No	No/No	Yes	Poor