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Tools for Measuring Human Lead Exposure

A Review of Methods and Implications for Future Research and Practice

RACHEL SILVERMAN BONNIFIELD · RORY TODD

Abstract

Exposure to lead has multifaceted negative impacts on human health and welfare. Estimates suggest that a third of the world's children have elevated blood lead levels (BLLs) exceeding 5 µg/dL. However, there is very limited data on the prevalence and severity of lead exposure, particularly within low and middle-income countries (LMICs), limiting understanding about the magnitude of the global lead poisoning crisis; the distribution of its severity; and the extent (if any) to which progress is being made. While the reasons for these data gaps are manyfold, a major constraint to better data collection is the unsuitability of established methods for blood exposure measurement, which can be too costly and impractical for many LMICs. As global lead poisoning receives more international attention, the challenge of identifying and implementing appropriate lead exposure measurement approaches for different purposes—including the monitoring, screening, and research required to prevent exposure, as well as clinical management in already exposed individuals—has received increasing recognition as a constraint to programmatic scale-up.

To inform ongoing efforts to scale-up global lead exposure prevention and mitigation, this paper reviews the state-of-the-science on the full spectrum of methods for measuring lead exposure in humans. Targeted to policymakers and others without technical scientific backgrounds, it first provides a high-level introduction to the science of lead exposure and related biomarkers, and presents a conceptual framework for evaluating lead exposure measurement methods that considers both the intrinsic characteristics of the method and the use case for measurement. It then reviews the state of the science for methods to measure *current* and *cumulative* lead exposure, including the strengths and weaknesses of specific methods. It concludes by evaluating the strengths and weaknesses of the overall portfolio of tools in aggregate, which in turn informs an agenda for further research and development.

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Background

Exposure to lead has multifaceted negative impacts on human health. Globally, lead poisoning is estimated to cause between 1.6 and 5.5 million deaths each year from elevated risk of cardiovascular disease; it also significantly impedes children's cognitive functioning, ability to learn, and future productivity.[i,ii] Estimates suggest that a third of the world's children have elevated blood lead levels (BLLs) above five micrograms per deciliter (µg/dL). (This reference level is commonly used to indicate elevated exposure, though lead has deleterious effects even at much lower levels and the US Centers for Disease Control have recently adopted a lower reference value of 3.5 µg/dL.) However, this high-level figure masks vast data gaps on the prevalence and severity of lead exposure, particularly within low and middle-income countries (LMICs), which are by far the most affected. This knowledge gap prevents policymakers and researchers from fully understanding the magnitude of the global lead poisoning crisis; the distribution of its severity; and the extent (if any) to which progress is being made.

At the national and local level, better data is essential to accurately capture the extent and distribution of lead exposure; motivate policymakers to act; and inform evidence-based interventions to reduce its burden. The case of Georgia is particularly instructive for why local data is indispensable. There, policymakers were spurred into action after UNICEF included a blood lead testing module in its 2018 Multiple Indicator Cluster survey (MICS), which revealed very high prevalence of lead poisoning among children, particularly in the west of the country.[iii] Notably, population data from Georgia significantly exceeded previous estimates from imputation, demonstrating the unreliability (at the national level) of current modelling vis-à-vis direct measurement. The subnational results from the population-level survey also provided suggestive evidence about one major cause of lead poisoning—specifically, adulteration of spices commonly consumed in western Georgia—which, alongside other evidence,[1] in turn informed a successful policy intervention to prevent the sale of adulterated spices. In the medium to long-term, Georgia is now working to increase its health sector's ability to diagnose, prevent, and treat lead poisoning, including by establishing better routine surveillance that can identify hotspots and surges in exposure.[iv]

Beyond Georgia, just two other LMICs (China and Mexico) have nationally representative data on lead exposure; a majority of LMICs have *zero* such data available.[v] The reasons for these data gaps are manyfold, and include lack of resources, as well as lack of awareness about lead poisoning and, consequently, lack of political prioritization of lead exposure measurement and surveillance. However, a major constraint to better, more consistent data collection is the unsuitability

1 In New York City, the municipal public health department also identified lead-adulterated spices, originating in Georgia, as a potential cause of elevated BLLs in Georgian immigrant communities. See Hore, Paromita, Kolapo Alex-Oni, Slavenka Sedlar, and Deborah Nagin. "A Spoonful of Lead: A 10-Year Look at Spices as a Potential Source of Lead Exposure." Journal of Public Health Management and Practice 25 (February 2019): S63.

of established methods for blood exposure measurement, which typically use a venous blood draw and laboratory analysis; these methods can be too costly and impractical for many LMICs. (For the Georgia MICS, for example, venous blood samples were shipped to Italy for analysis, given the paucity of local laboratory capabilities).[vi]

As global lead poisoning receives more international attention, the lack of data on lead exposure in LMICs—and the challenge of identifying and implementing appropriate lead exposure measurement approaches in those settings—has received increasing recognition as a constraint to programmatic scale-up.[vii] Several novel methods for measuring current lead exposure have recently been developed, which aim to offer similar levels of accuracy while being feasible to scale in low-resource contexts. There is also increasing policy interest in research and development for new, lower-cost point of care measurement tools; in order to best direct resources, policymakers and biotech researchers must better understand the deficits of existing options, and, in turn, the desirable characteristics of novel methods/potentially innovative approaches.[viii]

In parallel, there has also been experimentation with methods to measure long-term exposure. This can be a highly valuable tool for research into the effects of interventions on exposure levels, as well as into the long-term effects of lead poisoning. The relationship between cumulative lead exposure and increased risk of cardiovascular disease is of particular research and policy interest; the American Heart Association recently acknowledged lead exposure as a significant risk factor for adverse cardiovascular outcomes, but there remains significant uncertainty about how cardiovascular risk scales with exposure over the life course, e.g. the extent to which past versus present exposure drives the observed relationship.[ix] Several methods have been shown to approximate long-term lead exposure, but there remain questions over their accuracy and safety.

This paper reviews the state-of-the-science on the full spectrum of methods for measuring lead exposure in humans. It draws from a literature review and presentations prepared for a Technical Workshop on Methods to Measure Lead Exposure Technical Roundtable, convened by the Center for Global Development on January 16, 2024; please see Annex 1 for details of the event, including speakers and presentations.

Importantly, the note is targeted to policymakers and others without technical scientific backgrounds, and is limited in its scope and technical comprehensiveness. Its goal is to review the suite of tools available, convey the key advantages and disadvantages of each method in different settings, and discuss implications for policy innovation, without necessarily capturing all scientific nuances and technical details. The paper's scope is also limited to the technical methods for lead exposure measurement—and, even more narrowly, to the diagnostic tools and methods available for doing so. This narrow focus necessarily excludes other essential elements of lead biomonitoring and surveillance, including but not limited to sampling approaches; planning and sensitization

in partnership with governments, ethical review boards, and affected communities; and the practical and ethical dimensions of how biomonitoring data is subsequently used and communicated to affected individuals and communities, including potential ethical imperatives to offer mitigation and treatment to exposed populations.

This paper proceeds as follows. First, it provides a high-level introduction to the science of lead exposure and related biomarkers, helping orient a lay audience to how lead is absorbed by and processed in the body, and how this in turn relates to different exposure biomarkers. Second, it presents a conceptual framework for evaluating lead exposure measurement methods that considers both the *intrinsic characteristics of the method*, on the one hand, and the *use case* for measurement, on the other. Third, it reviews the state of the science for methods to measure *current* lead exposure, typically in the form of blood lead measurement, including the strengths and weaknesses of specific methods. Fourth, it reviews the state of the science for methods to measure *past* or *cumulative* lead exposure, noting substantial uncertainty in existing approaches. The paper concludes by evaluating the strengths and weaknesses of the overall portfolio tools in aggregate, which in turn informs an agenda for further research into the refinement of existing methods, as well as the development of novel approaches.

Part 1: Understanding the science of lead exposure and biomarkers

Lead is absorbed primarily through ingestion or inhalation, with a negligible amount entering through the skin.[x] Almost all inhaled lead is subsequently absorbed into the blood, but rates of uptake from ingested lead vary significantly, with children absorbing around 40–50% and adults only 5–10%.[xi] Whole blood lead levels are typically used for lead exposure measurement despite some challenges.[2] Whole blood lead levels (BLLs) are commonly reported in micrograms per deciliter (µg/dL) and widely used for surveillance, clinical management, and research; the significance of a range of different potential BLLs is contextualized in Table 1.

2 99% of lead in the blood is bound to red blood cell proteins; see US EPA, ORD. 'Integrated Science Assessment (ISA) for Lead'. US EPA, January 2024. However, there is some inconclusive evidence that blood in plasma may have greater toxicological impact; see Hu, Howard, Regina Shih, Stephen Rothenberg, and Brian S. Schwartz. "The Epidemiology of Lead Toxicity in Adults: Measuring Dose and Consideration of Other Methodologic Issues." Environmental Health Perspectives 115, no. 3 (March 2007): 455–62. Plasma lead levels are far more difficult to measure than whole blood lead, due to the comparatively low concentrations of lead in plasma.

TABLE 1. Contextualizing blood lead levels and their clinical significance

Blood Lead Level (µg/dL)	Significance
0.016	Preindustrial level.[xii]
0.6	Median levels for children aged 1–5 in the U.S.[xiii]
3.5	95th percentile for children in the U.S., used by the CDC as a reference value to designate 'exposed' individuals.[xiv]
5	Reference level previously used by CDC, and still in use internationally, including the WHO 2021 Guideline for Clinical Management of Exposure to Lead.[xv] Decreased cognitive function, increased prevalence of attention deficit hyperactivity disorder and increased antisocial behaviour.[xvi] Note that even levels below 5 µg/dL may have these effects—no level of lead is safe.
10	Hypertension, possible increased preterm birth, possible increased spontaneous abortion, among other symptoms.[xvii]
15	Median levels in the U.S. in 1976, the first survey of blood lead levels by the National Center for Health Statistics.[xviii]
>45	Chelation therapy recommended by WHO in children under 10 years old.[xix]
>80	Potential encephalopathy.
>105	Severe neurological symptoms.[xx]
100–200	Potential death.[xxi]

Lead in blood has a relatively short half-life, measuring around 35 days for adults and somewhat less for children.[xxii] For this reason, blood lead level (BLL) measurement is typically used to indicate current or recent exposure to lead. In turn, an individual's blood lead level can be a relatively volatile and imprecise measure of their general cumulative exposure levels over time, especially if lead exposure follows seasonal or irregular temporal patterns; this is sometimes addressed by collecting several samples spaced over time, and calculating a weighted average, known as a Cumulative Blood Lead Index (CBLI).

Once absorbed in the blood, a majority of blood lead is excreted through the kidneys or liver, but some lead is absorbed into soft tissue, from where it is subsequently remobilized into the blood in the following days and weeks. A small portion of blood lead is ultimately stored in bone, which serves a "semi-permanent" long-term storage; in adults, this gradual cumulative exposure means that around 94% of lead in the body is contained in bone and teeth.[xxiii] Cumulative exposure is therefore most commonly measured through bone lead. Bone lead can then be remobilized into the blood over the course of an individual's life, especially during metabolic processes such as those triggered by pregnancy and osteoporosis.[xxiv] In chronically exposed individuals, this remobilization means that blood lead levels may take quite a long time–months or potentially several years—to decrease following a reduction in present lead exposure.[xxv] In cases where lead is being remobilized from bones, blood lead levels may not necessarily reflect recent lead exposure.

Like bone lead, lead in teeth builds up slowly over time. Some studies have suggested that teeth may be a more reliable biomarker for cumulative lead exposure, as the body is less likely to remobilize lead stored in teeth than in bone.[xxvi] There is a clear difference between prenatal and postnatal dental tissue, allowing exposure before and after birth to be distinguished.[xxvii] Studies have demonstrated strong correlations between the lead in different dentine layers and blood lead at different timepoints in an child's life. This suggests that the spatial distribution of lead in teeth can potentially be used to understand the history of lead exposure over the course of an individual's life, although there is still uncertainty about the accuracy of this approach in practice.[xxviii] Both bone and teeth lead are typically measured in micrograms of lead per gram (µg/g), but their relatively infrequent use means that they lack clear reference levels.

There are several other potential biomarkers of lead exposure, but they are thought to be substantially more unreliable than the biomarkers described above, and there are no available reference levels to which results can be compared. Saliva, which is by its nature very easy to sample, varies substantially in its ion content, depending on the time of day, and on individual characteristics.[xxix] It is also more vulnerable to external contamination, and recent studies have found weak correlations between saliva lead levels and blood lead levels.[xxx] Hair is affected even more strongly by the risk of external contamination, and the window of exposure that it can reflect is unclear.[xxxi] A 2005 review of biomarkers concluded that there were several issues which needed to be addressed before hair could become a viable biomarker for heavy metals.[xxxii]

Part 2: Conceptual framework for evaluating lead exposure measurement methods

Different measurement approaches for human lead exposure differ dramatically in their characteristics, including accuracy, precision, cost, timeliness of results, infrastructure requirements, and more. While these characteristics will vary across methods, the suitability of any given measurement approach for lead exposure is not fixed, but instead depends on the *needs* and *resources* of the party doing the measurement. There are many possible reasons for why a researcher or policymaker would want to understand lead exposures—and different methods will be more or less suitable for different use cases.

This section offers a conceptual framework for evaluating lead exposure measurement methods that considers both the *use case* for a given measurement exercise, on the one hand, and the *intrinsic characteristics of the method*, on the other. In its first part, it lays out the range of potential use cases for lead exposure measurement, with some discussion of what this would imply for measurement needs. In the second section, it considers the intrinsic characteristics of different measurement techniques and what this implies for their performance against different use cases in resource-constrained settings.

Use cases for lead exposure measurement

There are several distinct reasons for why a clinician, policymaker, or researcher may want or need to measure lead exposure:

- ### *Clinical management of lead poisoning*

  Most directly, levels of lead exposure have clinical significance: the magnitude of an individual's present exposure is used to guide their treatment. For example, measurement of blood lead in individuals with suspected acute lead poisoning is of direct clinical relevance in determining whether chelation therapy should be administered. (Under conditions of high exposure, i.e. >45 µg/dL, the WHO recommends that all children below the age of ten undergo chelation therapy, while at intermediate levels, i.e. 40–45 µg/dL, chelation should be considered.)[xxxiii] Blood lead measurement to inform clinical management must be accurate, precise, and timely, as well as cost-effective and feasible for the local health system in which it is administered. (Separately, the health system must also have capacity to provide appropriate interventions to treat and prevent exposures, including by removing the original exposure source and providing chelation therapy where it is clinically indicated.)

- ### *Screening for elevated blood lead levels*

  As most lead exposure is not clinically evident, it is often desirable—especially in contexts where lead exposure is widespread—to screen wider groups, potentially entire populations, who show no *ex ante* symptoms of lead exposure, and then intervene to prevent/address continued lead exposure in those who show elevated exposure levels. Because screening needs to be applied to a broad population without a known problem, affordability and at-scale feasibility and acceptability of the testing method is of particular concern; however, policymakers may be willing to compromise with lower precision and less timely results. Screening may be population-wide, or focus on specific subpopulations expected to be at higher risk of lead exposure, for example occupationally exposed populations such as those working in battery recycling facilities. In the case of a high initial reading from a capillary blood sample, more precise blood lead testing methods may be used in follow-up to confirm the result.

- ### *Monitoring and surveillance*

  At a regional or national level, policymakers need to measure population-level lead exposure to understand the prevalence and patterns of exposure; form initial hypotheses about sources of lead exposure; inform the prioritisation of lead poisoning among other public health challenges; and to track exposure levels over time, which can in turn enable evaluation of the effects of public health interventions. As with screening, this implies a need for testing methods which are low-cost, broadly acceptable, precise, and relatively easy and simple to administer at scale; however, timeliness of results is less critical. Monitoring approaches should account for the

possibility of seasonal variation, as exposure levels in spring and summer can systematically differ from levels in the same populations in winter.

In most countries, there is currently no reliable data on population exposure levels, so collecting baseline data, potentially via one-off surveys, is a short-term priority. In the long-term, there is a need to establish sustainable surveillance systems to monitor blood lead levels as well as population exposure to other environmental pollutants. Here one can distinguish between 'active' surveillance— in which blood lead levels are monitored through periodic surveys of a representative sample of the population—and 'passive surveillance'—in which population levels are monitored through reports received from healthcare providers or laboratories, which routinely conduct blood lead level testing for their own clinical purposes or to fulfill legal obligations.[xxxiv,3]

- ***Research***

Measurement of lead exposure is required for most[4] medical, economic, or social science research on the causes, sources, and effects of lead poisoning. This includes research where lead exposure is the dependent variable for a social phenomenon or policy intervention (e.g., what is the effect on blood lead levels associated with eliminating leaded gasoline?), as well as research in which lead is the exposure variable of interest for health or social outcomes (e.g., what is the effect of lead exposure on cardiovascular disease or delinquency?). There is limited evidence on what works to reduce lead exposure, especially in low and middle-income countries, and in many cases the primary sources of exposure are still unknown. Similarly, while there is a wealth of research on the effects of lead on health and cognitive outcomes, questions still exist over the magnitude of these effects, as well as the validity of other hypothesized effects on conditions including Amyotrophic Lateral Sclerosis and Alzheimer's disease.

The best-suited method will depend on both the research question and study design. As discussed in Part 4, measures of cumulative exposure allow for retrospective research designs which would not be possible with measures of present exposure. To inform research, which will in turn be used to inform policy for millions or billions of people, there is a need for very high precision of measurement, with less of an emphasis on affordability or timeliness.

3 For example, in the United States, every child receiving Medicaid is legally required to receive BLL testing at 12 and 24 months of age; the results of these tests inform clinical practice and are also reported to central surveillance databases (e.g., passive surveillance). See CDC. "CDC National Childhood Blood Lead Surveillance Data". Accessed 2 May 2024. https://www.cdc.gov/nceh/lead/data/national.htm.

4 Note: It is possible to conduct some research on the effects of lead exposure without ever directly measuring lead exposure levels, e.g. via reduced form natural experiments or randomized controlled trials, for example Litzow et al. 2023. However, lead exposure measurement may be desirable even in such cases to confirm the observed causal pathway and observed dose response relationship.

- ***Establishing liability***

  Another motivation for measuring lead exposure levels may be to establish legal liability or other responsibility for the exposure and consequent deleterious effects. For example, a plaintiff may wish to establish the liability of an industrial site by measuring present exposure levels of communities living closer to and further away from the facility. Developments in the measurement of lead in teeth or bone have opened up the possibility of measuring past exposure levels at different points in an individual's development, ideally accompanied by detailed exposure histories. This has potential implications for legal cases involving lead, by allowing for the timepoint of exposure to be identified. Any measurements used to establish or infer legal liability must necessarily have high levels of accuracy and precision.

Characteristics of measurement approaches and performance in resource-constrained settings

In considering the merits and drawbacks of the methods currently available for measuring blood lead levels for different use cases in a resource-constrained environment, it is useful to think about how they perform on the following dimensions:

-  **Cost:** Given the fiscal constraints of many low and middle-income countries, there is a need for low-cost testing methods which are affordable to roll out at scale in the local context. Cost evaluations should consider both the marginal cost of each test and any up-front costs of the testing method, which may include equipment procurement or construction of new laboratories. (These considerations are considered under 'Equipment Requirements'.)

-  **Personnel Requirements:** Testing technologies differ substantially in the time and expertise required of operators, which presents a potentially significant cost and/or constraint in countries with fewer trained medical and laboratory personnel. Trained personnel may be required for both collection and analysis of specimens.

-  **Equipment Requirements:** Many low and middle-income countries lack laboratories capable of high-complexity analytical methods, and/or the specific equipment required for certain types of lead exposure measurement. It can also be challenging to source reagents and other consumables in some LMICs. The potentially stronger risk of cross-contamination in urban and industrial settings in LMICs also means that laboratories must take extra care to ensure samples are not invalidated. In some cases, equipment constraints may be circumvented by transportation of samples to another country, as was done recently in Georgia;[5] however, sample export is likely too costly and time-consuming for clinical applications or routine monitoring.

5 UNICEF Georgia. 'How UNICEF Is Ending Childhood Lead Poisoning in Georgia'. UNICEF. 21 February 2024. https://www.unicef.org/georgia/stories/how-unicef-ending-childhood-lead-poisoning-georgia.

-  **Logistical requirements:** Technologies differ in how tests are processed. Specifically, tests using some measurement methods may need to be transported to a laboratory for analysis. To do so effectively and reliably requires certain transport infrastructure, which may not be available in some contexts.

-  **Precision and Limit of Detection:** Precision varies significantly across technologies, and between laboratories practising the same technology. Related but distinct is a technology's 'Limit of Detection', the lowest level at which the uncertainty of the measurement is less than its magnitude. The need for a low limit of detection will vary depending on the use case. For example, screening for high exposure levels would not require an especially low limit of detection. A survey tracking changes in general population exposure levels over time, however, would need to be able to differentiate small differences at low levels of blood lead. Here the more relevant measure is a technology's limit of quantification, the lowest level which can be reliably quantified, which will generally be higher than the limit of detection.

-  **Risk of Contamination:** The abundance of lead in the environment means that contamination is a frequent issue, and steps must be taken with all methods to curtail this risk in order to avoid invalid results. Contamination can occur when blood is taken, particularly in the case of capillary blood samples, which risk contamination from the surface of the skin. Collection supplies can also be contaminated with lead; ideally, collection supplies should be validated before use to ensure there is little to no contamination. Laboratory methods using "gold standard" venous blood testing greatly reduce the risk of contamination, but at a relatively high cost both financially and with respect to logistical and personnel needs.[6]

-  **Timeliness of Results:** Delays in obtaining results after collection can slow down required treatments and interventions to prevent further exposure. This may be a function not just of the measurement method used, but also the IT infrastructure and levels of connectivity between the Primary Health Care system and patients. Point-of-care tests, which produce results immediately within the clinical setting, are generally considered desirable within healthcare as they can in theory pre-empt the need for remote follow-up and enable prompt treatment/management. (In practice, however, available point of care tests for lead exposure may not be sufficiently reliable or precise to inform treatment without confirmatory testing of a venous sample.)

-  **Ethics and Acceptability:** Broadly speaking, measurement of lead exposure must be done in a manner that is aligned with medical ethics/informed consent, and which is acceptable to the patient population. The ethical considerations are especially heightened for testing of children, who are often the population of interest for

6 Note: The Centers for Disease Control and Prevention runs a proficiency program (the Lead and Multielement Proficiency Program) to evaluate how well laboratories follow protocols to improve accuracy. This has had an important role in quality-assurance for national laboratories, and thirty international laboratories which participate.

lead exposure. A comprehensive treatment of all ethical and acceptability dimensions of testing is beyond the scope of this paper, but such considerations may inflect, for example, the choice of venous vs. capillary blood sampling. (Venous samples, being generally more invasive, are more likely to be viewed with suspicion or refused by children or their parents, requiring more extensive patient sensitization efforts.) Testing requires full informed consent from adults and parents, which may require planning when in a low-resource setting. Any testing exercise must also carefully consider the ethical dimensions of how results—particularly, findings of elevated blood lead levels—are communicated to individuals and parents, and how such results are subsequently addressed with treatment, exposure reduction, and/or other interventions. (It may be considered unethical to conduct testing exercises without being able to address cases of lead poisoning identified through those exercises.) These concerns should be assessed by an ethics board before testing begins.

Part 3: Measuring current exposure

As discussed in Part 1, an individual's present or recent exposure to lead is typically measured using their blood lead level (BLL), generally presented in micrograms of lead per deciliter of blood (µg/dL). There are several potential approaches to collecting blood lead levels, and the most suitable method will depend on both the primary objective of blood collection and the resources available in each setting.

There are two primary ways in which blood testing methods differ: first, in the method by which blood is collected, stored and/or transported, and second, in the method by which blood is analysed.

Methods for sample collection

There are two primary methods of sample collection for blood lead testing: venous blood draws, which are considered the "gold standard" in terms of accuracy, precision, and limit-of-detection; and capillary blood draws, which offer increased convenience with some drawbacks, as detailed below:

Venous blood draw

The gold standard sample collection method for accurate blood lead testing is through venipuncture. This approach minimizes risks of sample contamination by lead on the surface of the skin. Venipuncture must be carried out by a trained phlebotomist, and venous samples can only be analysed in a laboratory setting. The requirement for laboratory analysis increases the time until results are received, while both of these requirements can present major constraints to testing in LMIC settings with limited heath worker and laboratory density. Venous blood lead

testing often uses collection tubes specifically designed to have low lead levels, for trace element testing.[xxxv] Typical sample sizes are 1.5 ml of blood;[xxxvi] after collection, samples are generally refrigerated until analysis, although studies have tended to find that lead is stable at room temperature for several weeks.[xxxvii]

Compared to capillary collection (discussed below), venous blood draws have higher risk of potential complications to the patient,[xxxviii] although serious reactions are still relatively rare (fainting occurs in 1–5.3% of patients).[xxxix] They are also more likely to result in discomfort and possibly refusal by patients and caregivers (e.g., of children).[xl] However, the larger volume of blood can enable potential quality assurance through testing duplicate samples, as well as other tests applied to the same sample, e.g. for anaemia as well as other heavy metals and/or micronutrients. This may offer a significant advantage in some cases, e.g. for household surveys that aim to assess general population health and exposures.[xli]

Capillary blood draw

In a capillary blood draw, a few drops of blood are taken by finger prick, or a heel prick in newborns and infants. Capillary blood draws do *not* require trained phlebotomists and therefore can be administered more easily in settings with relatively few health workers. The first drop is discarded as it is more likely to be contaminated by tissue fluid or sloughing skin.[xlii] To lower the risk of external contamination, the finger should be thoroughly washed before collection; nevertheless, there is still a significant risk of sample contamination by lead on the skin. Once the finger has been pricked, blood can be collected with a microcontainer tube, a glass capillary tube which has been treated to prevent coagulation (as used by the LeadCare II test), or dabbed onto a Dried Blood Spot (DBS) card.

In general, patients report less discomfort from capillary compared to venous blood draws,[xliii] although there is potential pain involved with the squeezing and application of pressure often required to draw blood, particularly by less trained personnel. Unlike with some venous blood collection tubes, capillary blood collection supplies are also not manufactured for trace testing, and therefore the risks of contamination from equipment are higher. Given the risks of contamination from several different sources, it is often recommended that findings of elevated blood lead levels from a capillary sample should be subsequently confirmed via a venous blood draw.

While Dried Blood Spot cards offer convenience, there is a higher risk of contamination, both through the production of the paper, and during the process of drying the sample. It can also be difficult to control the volume of blood collected; this can cause "hematocrit bias," as blood with a higher volume percentage of red blood cells tends to spread less on the paper, meaning that a higher volume of blood is taken within the same fixed-diameter sub-punch.[xliv] In recent years, two technologies have been developed to address this specific challenge. A first technique, Volumetric Absorptive Microsampling (VAMS), uses an absorptive tip to take a fixed volume of blood.[xlv] A second technique uses filter paper with microfluidic technology to regulate the amount of blood absorbed in Dried Blood Spots.[xlvi]

Analysis

Once taken, there are several options for analysing levels of lead in blood.

Graphite Furnace (or electrothermal) Atomic Absorption Spectrometry (GFAAS)

Graphite Furnace (or electrothermal) Atomic Absorption Spectrometry (GFAAS) involves vaporizing the sample in a graphite-coated furnace, and monitoring the wavelengths of light which are absorbed from a light source.

Sample Type: Capillary or venous. However, the details below refer to GFAAS applied to venous blood samples.

Marginal Cost: Highly variable and challenging to quantify.

Personnel Requirements: The US CLIA considers GFAAS a high-complexity test, meaning that it requires significant training and laboratories must participate in proficiency testing.

Equipment Requirements: Instruments cost between $30,000 and $50,000. Tests require reliable energy and water sources, as well as Argon gas and reagents, which can be difficult to source in LMICs.

Logistical Requirements: Must be transported to a laboratory for analysis.

Precision and Limit of Detection: A recent review found a limit of detection between 0.2 and 1 µg/dL.[xlvii] Proficiency testing data between 2010 and 2019 found a site-to-site variability of 1.6 µg/dL for laboratories in the United States, for sample concentrations between 3 and 4.1 µg/dL, demonstrating that the very best laboratories can perform significantly better than average.[xlviii]

Risk of Contamination: Risk of contamination is low provided that a tube manufactured for lead or trace metals is used.

Timeliness of Results: 2 to 3 minutes, but only after samples have been transported to a laboratory.[xlix]

Ethics and Acceptability: For high-accuracy tests, requires relatively invasive venous blood draw.

Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

More recently, there has been a shift in laboratory methods to inductively coupled plasma mass spectrometry (ICP-MS). ICP-MS is even more precise and sensitive than GFAAS, meaning that it is commonly seen as the 'gold-standard' method for blood lead level analysis. It also allows for multiple elements to be analyzed at once.

Sample type: Capillary or venous. However, the details below refer to ICP-MS applied to venous blood samples.

Marginal Cost: Highly variable and challenging to quantify.

Personnel Requirements: ICP-MS requires highly-skilled laboratory technicians. ICP-MS is also a high-complexity test, meaning that laboratories must participate in proficiency testing.

Equipment Requirements: Instruments cost between $150,000 and $300,000. Tests require reliable energy and water sources, as well as Argon gas and reagents, which can be difficult to source in LMICs.

Logistical Requirements: Must be transported to a laboratory for analysis.

Precision and Limit of Detection: The protocol used by the Centers for Disease Control and Prevention (CDC) has a lower limit of detection of 0.049 µg/dL, which is the lowest limit-of-detection of any technology.[l] Lab-to-lab variability is lowest in proficiency testing among labs using this test type (e.g., +/−0.83 µg/dL for sample concentrations between 3 and 4.1 µg/dL).[li]

Risk of Contamination: Risk of contamination is low provided that a tube manufactured for lead or trace metals is used.

Timeliness of Results: 0.5 to 3 minutes, but only after samples have been transported to a laboratory.[lii]

Ethics and Acceptability: For high-accuracy tests, requires relatively invasive venous blood draw.

LeadCare II

LeadCare II, currently the only CLIA-waived point-of-care test for blood lead, uses a technology called Anodic Stripping Voltammetry.[7] Blood from a glass capillary tube which has been treated to prevent coagulation is mixed with a reagent and dispensed onto a sensor strip, which is then inserted into a portable LeadCare II analyzer. All of this can be done at the point of care, allowing for results to be obtained in three minutes.

Sample Type: Capillary.

Marginal Cost: A single test kit costs around $10, although this can vary significantly by location and provider.[liii] This may be inflated due to the monopoly on the technology by Meridian BioScience; costs may decrease after patents expire.

7 CLIA refers to the Clinical Laboratory Improvement Amendments of 1988, which required that laboratories conducting high-complexity tests be certified by the Department of Health and Human Services. Waived tests are those below the complexity threshold and therefore with less risk of error, meaning they are cleared by the FDA for home use and their use does not need to be certified. https://www.cdc.gov/labquality/waived-tests.html.

Personnel Requirements: LeadCare II uses a capillary blood sample, meaning that there is no requirement for a phlebotomist. Users can conduct tests after consulting the test instructions.[liv]

Equipment Requirements: A LeadCare II analyzer is currently priced around $3000.[lv] The system is very portable at just over one kilogram in weight, and can be run on batteries. However, test kits have a relatively short shelf-life, which can cause issues for large-scale surveys.[lvi] There are also limits on temperature and elevation, limiting the system's useability in many LMIC settings.[lvii] Finally, the system has been subject to past recalls, casting some uncertainty on the reliability of results.[lviii]

Logistical Requirements: Samples can be taken and analyzed at the point of care, meaning that there is no requirement for refrigeration or transportation (in fact refrigeration invalidates blood samples), and patients can receive results immediately; this negates the requirement for a system to report results back to patients. Samples can be kept for twenty-four hours before analysis.

Precision and Limit of Detection: Limit of detection is fixed at 3.3 µg/dL.[lix] Proficiency testing data show site-to-site variability of +/–1.8 µg/dL for sample concentrations between 3 and 4.1 µg/dL, only slightly higher than GFAAS although substantially higher than ICP-MS.[lx]

Risk of Contamination: There is a significant risk of contamination, due to the use of a capillary sample. Thorough hand washing can reduce the chances of contamination from lead on the skin, but there are still risks from the ambient environment.

Timeliness of Results: Three minutes, and available at point-of-care. However, it is not possible to automate this process; this implies that while for small studies and individual patients LeadCare II may have a substantial time advantage, for large-scale studies it may not speed up data collection compared to laboratory methods.

Ethics and Acceptability: Capillary blood samples are in general far more acceptable to parents and communities. The fast turn-around times for results also means that information can be immediately shared with patients and/or their parents.

LeadCare Plus and LeadCare Ultra

LeadCare Plus and LeadCare Ultra are similar technologies to LeadCare II, but with more complex requirements; in the United States, they are not CLIA-waived (and therefore are not approved for point-of-care testing). This also means that samples must be transported to and analysed in a laboratory. Capillary samples can be kept refrigerated and used within a 72-hour period.

Sample Type: Capillary.

Marginal Cost: A single test costs around $15, but this may vary by location and provider.[lxi]

Personnel Requirements: Requires some lab training, although less than the high-complexity tests (GFAAS and ICP-MS).

Equipment Requirements: LeadCare Plus device cost is approximately $3,500, while the LeadCare Ultra costs around $25,000. The laboratory must provide its own pipette. As with high-complexity tests, users in the United States must participate in proficiency testing.

Logistical Requirements: Blood must be stored from 1C–25C from collection until analysis.

Precision and Limit of Detection: Limit of detection is fixed at 1.9 µg/dL for both technologies.[lxii] There is a lack of evidence on site-to-site variability in practice.

Risk of Contamination: There is a significant risk of contamination, due to the use of a capillary sample.

Timeliness of Results: After a sample is transported to the laboratory, results can be obtained within 3 minutes. LeadCare Ultra, unlike LeadCare Plus and LeadCare II, can process six samples at a time.

Ethics and Acceptability: Capillary blood samples are in general far more acceptable to parents and communities. As samples must be transported to a laboratory, there must be a system for communicating results to patients and parents.

XRF with Dried Blood Spots (DBS)

Recently, there has been experimentation with using X-Ray Fluorescence (XRF) to analyse Dried Blood Spots for lead levels.[lxiii,lxiv] XRF methods direct x-rays at a material to excite electrons and release a small amount of energy, which can be measured and used to infer its elemental composition. Currently, energy-dispersive-XRF and Total XRF have been trialled, with promising results. Some devices are portable, potentially allowing for point-of-care testing.

Sample Type: Capillary.

Marginal Cost: There is a small cost associated with the dried blood spot card, and materials used to digest the sample for Total XRF.[lxv] There are no marginal costs for energy-dispersive-XRF besides a negligible amount of electricity.

Personnel Requirements: Depending on the type of XRF technology used, some level of laboratory expertise may be required.

Equipment Requirements: Machines cost between $75,000 to $110,000 for energy-dispersive XRF, and $120,000 to $140,000 for Total XRF.[lxvi] XRF analyzers also have limited lifespans, meaning equipment costs can accumulate over time.

Logistical Requirements: If analysis occurs in a laboratory, the sample must be transported, although not necessarily at a low temperature. If portable technology is used, then no transportation is necessary, as analysis can be conducted at point of care.

Precision and Limit of Detection: For Total-XRF, there is a limit of detection between 0.59 and 2.23 µg/dL.[lxvii] For energy-dispersive XRF, a current limit of 1.7 µg/dL has been established in the published literature.[lxviii] This method measures the whole blood spot, which can counter the 'hematocrit' bias from using Dried Blood Spots due to differential spreading of blood.

Risk of Contamination: Risk of contamination is moderate to high, as there are risks from both the skin during collection, and from the card during its production and the blood drying process.[lxix] One proposed method to address the risk of contamination during drying is using volumetric collection, which would not require drying, although this does not address risks of contamination from the paper production process. Similarly, researchers have experimented with correcting for background contamination from the card by measuring a different part of the card; however, contamination across the card may not be constant.[lxx]

Timeliness of Results: Requires blood spot to dry, and for most precise measurements, an analysis time of ~30 minutes. Analysis time can be significantly shortened with more powerful devices; existing systems have reduced this to nine minutes.

Ethics and Acceptability: Capillary blood draw is more likely to be acceptable to parents and communities. Turnaround time is not as low as with LeadCare II, but the process is still relatively fast.

Part 4: Measuring cumulative exposure

Data capturing an individual's long-term exposure to lead is of great importance for research into both the causes and effects of lead exposure. Prospective cohort studies can generate such data over a long-term time horizon by conducting regular BLL measurements at multiple time-points. However, it may also be necessary or desirable to generate data about the long-term exposure of current populations, for whom past BLL data was not regularly collected/is not available. In these circumstances, measurements of an individual's *cumulative exposure* can act as a proxy, allowing for research designs which might otherwise be impossible. For example, measures of cumulative exposure can facilitate retrospective studies using "natural experiments," in which some external event—for example, a change in water source for one neighbourhood—differentially affects lead exposure levels in different parts of a population. Under certain conditions, "natural experiments" can estimate the effects of lead exposure with a stronger claim to causation than standard associational studies.

Another potential application of long-term exposure measurement is in assessing the contribution of different sources to overall exposure. Given the wide range of possible sources of lead exposure, it can be difficult or impossible to identify the relative contribution of each source vis-à-vis total exposure for an individual or community. The capacity to measure exposure at different points in the past may be helpful for this purpose. For example, knowing whether exposure in a community increased after an industrial site was established would provide evidence about the extent to which the site increased the community's lead exposure. This information could theoretically help to apportion liability in particular cases, as well as aid policymakers in determining the most significant sources of exposure and identifying effective policy interventions to reduce it, though the legal and ethical requirements for doing so are beyond the scope of this paper.

BOX 1. Reference values for long-term lead exposure levels

Both bone and teeth lead are typically measured in micrograms of lead per gram of tissue. In some cases tooth lead may be expressed as a ratio with calcium levels, in order to control for variation in mineral content between samples; this presents a potential additional source of variability, if calcium levels compete actively with lead levels. As research on bone and teeth lead is comparatively undeveloped, they lack reference values equivalent to those used with blood lead testing. In the US, recent large-scale studies have estimated average tibia bone levels between 8.8 µg and 20.27 µg/g.[lxxi,lxxii]

The primary methods for measuring long-term lead exposure use bones and teeth as biomarkers, and are addressed in detail below:

Bone

As discussed in Part 1, a significant majority of lead in the body is contained in bone, where it accumulates over the course of an individual's life. Estimates suggest that the half-life of lead in bone ranges from ten to thirty years; bone lead is therefore the most commonly used biomarker to assess cumulative exposure. There are two 'types' of bone that can be measured: cortical bone, which is the dense, solid tissue surrounding the marrow; and trabecular bone, which is less dense and intersperses the bone marrow compartment. Trabecular bone exchanges more rapidly with blood than cortical bone, meaning that it is less strongly reflective of long-term exposure.[lxxiii] Cortical bone lead is typically measured using the midpoint of the tibia, while trabecula bone is measured using the patella or calcaneus.[lxxiv]

The obvious challenge to measuring bone lead is sampling. Taking a biopsy, while theoretically possible, is an extremely invasive and potentially risky procedure. An alternative is posthumous analysis, but this presents obvious limitations.

Bone lead is therefore almost always measured using X-Ray Fluorescence Spectrometry (XRF), the principles of which are described in Part 3.

K-XRF

Historically, the most common XRF variant has been K-XRF, which excites electrons on the K-shell of atoms. This method allows the analysis to penetrate the bone and therefore measure both cortical and trabecular bone lead. However, K-XRF sampling of bone lead requires cumbersome equipment and can take up to 30 minutes per reading.

Marginal Cost: Negligible.

Personnel Requirements: Requires significant training to deploy.[lxxv]

Equipment Requirements: Machine cost between $60–100K. An additional issue is that the radioactive isotope used for this technology, cadmium-109, is only possible to source from Russia.[lxxvi] The war in Ukraine has therefore made use of this technology considerably more difficult.

Logistical Requirements: Stationary instrument requires sampling to be conducted at a central location.

Precision and Limit of Detection: Limit of detection of 2–10 µg/g.[lxxvii] Precision deteriorates as the radioactive source decays.[lxxviii]

Risk of Contamination: Negligible.

Timeliness of Results: 30–40 minutes.

Ethics and Acceptability: There is some concern about radiation from XRF devices, but in practice the radiation levels appear to cause minimal risk. A dosimetry study of K-XRF found effective dose values for one-year olds to be around 1.1 µSv.[lxxix] (As the International Commission on Radiological Protection (ICRP) recommends a limit to the public of 1000 µSv per annum, XRF analysis should not represent a significant contributor unless repeated measures are taken within a short time-interval.[lxxx]) Nevertheless, subjects should be informed of the risk, however minimal, to in turn offer their informed consent.

L-XRF

More recently, studies have successfully deployed L-XRF—exciting the electrons on the L-shell of the atom—which uses low-weight, handheld equipment and can be read in minutes. The limit-of-detection has in the past been significantly higher for L-shell XRF, although recent developments have pushed this limit down substantially.[lxxxi] Due to the low-energy X-rays it uses, L-XRF cannot penetrate very far and can therefore only measure cortical bone, not trabecular bone.

Marginal Cost: Negligible.

Personnel Requirements: Can be trained within a few hours.[lxxxii]

Equipment Requirements: Machine cost between $30,000–45,000.[lxxxiii]

Logistical Requirements: Portable instrument allows for point-of-care testing.

Precision and Limit of Detection: Previous limits of detection were 7–10 µg/g.[lxxxiv] Recent unpublished research suggests lower limits of 0.6 to 2.75 µg/g.[lxxxv]

Risk of Contamination: Negligible.

Timeliness of Results: 3–5 minutes.

Ethics and Acceptability: A dosimetry study of the use of L-XRF to measure bone lead found that typical procedures resulted in a total body effective dose of 3.4 µSv.[lxxxvi] While higher than that for K-XRF, this dose is still relatively low.

BOX 2. Insights from provocative chelation

During *provocative chelation*, a healthcare provider administers a chelation drug such as DMSA or EDTA to a patient or subject, and subsequently measures excreted lead in their urine. While side-effects from chelation have been the subject of attention in the past, recent evidence from the Trial to Assess Chelation Therapy (TACT) suggests that chelation is generally safe in adults.[lxxxvii] The levels of excreted lead may be broadly indicative of long-term exposure, but the exact meaning of the measurement remains unclear. (DMSA-chelatable lead, specifically, has been described as an estimate of *bioavailable* lead stores, rather than a comprehensive measure of long-term exposure.) Provocative chelation is also in some ways less practical than other methods, as urine sampling must take place several hours after administration. Given this, as well as improvements in methods to measure lead in bone and teeth, provocative chelation is not dealt with in detail here.

Teeth

For measurement of long-term exposure, teeth offer the primary sampling alternative to bones. Some studies suggest that teeth have better potential than bones as a long-term biomarker, as lead is remobilized from teeth at an even slower rate.[lxxxviii] In addition, a 'neonatal' line in teeth tissue demarcates tissue developed before and after birth, making it easy to distinguish pre and post-natal exposure.[lxxxix] Practically, an advantage for use of teeth as a biomarker is the natural loss of "baby teeth" in childhood and early adolescence; this could in theory make sampling for young children relatively straightforward, though there may nevertheless be significant ethical and practical considerations in acquiring samples for research and analysis. (For older children and adults, however, acquiring teeth samples presents similar issues to testing of bone.)

Lead levels can be measured in both dental *enamel*, which is the hard, visible tissue which covers the crown, and *dentin*, which is the less mineralized tissue underneath it. Unlike measuring lead in dentin, which can only be practised on teeth which have fallen out or been extracted, it is possible to measure enamel lead levels *in vivo* through Surface Dental Enamel Acid Etch Microbiopsy, described below. However, there remains debate over how well enamel measures reflect cumulative lead exposures.[xc] More broadly, the literature on practical usage of these approaches is still very limited, and existing papers do not report against the entire suite of performance criteria used in this paper.

There has also been initial experimentation with use of XRF for lead measurement in teeth; as this research is comparatively undeveloped, it is not dealt with here.[xci]

Surface dental enamel acid etch microbiopsy

This method samples lead in the enamel, and importantly, can be conducted *in vivo*. After teeth are thoroughly cleaned, an acidic solution is applied to a small window on the tooth's surface for 35 seconds.[xcii] The resulting solution is then rinsed, combined with a re-agent, and lead is measured through Graphite Furnace Atomic Absorption Spectrometry or another laboratory method.[8]

Marginal Cost: Material costs are very low.[xciii]

Personnel Requirements: Requires significant expertise in dentistry to conduct safely.[xciv]

Equipment Requirements: Significant dentistry and scanning equipment required.

Logistical Requirements: Not reported.

Precision and Limit of Detection: Limit of detection of 12 µg/g, but precision can be impacted by the requirement of normalizing levels to calcium.[xcv]

Risk of Contamination: Teeth cleaning preparation reduces the likelihood of exogenous contamination, but some risk of contamination remains, as contaminants can be diffused from the saliva. As with other methods, care must be taken to prevent the contamination of samples, including ensuring that materials are lead-free.

Timeliness of Results: Biopsy time is less than a minute. Scanning takes approximately half an hour.[xcvi]

Ethics and Acceptability: Requires consent to carry out sampling.

8 More information on this procedure can be found in: Olympio, Kelly Polido Kaneshiro et al. "Can in Vivo Surface Dental Enamelmicrobiopsies Be Used to Measure Remote Lead Exposure?" Environmental science and pollution research international 25.10 (2018): 9322–9329.

Laser Ablation-Inductively Coupled Plasma-Mass Spectrometry

This method can be used to measure lead levels in both the enamel and dentine. Teeth must be extracted (or fall out naturally), and then sectioned using a saw. Samples are cleaned and then sampled using laser ablation, which negates the need to pulverize teeth. Analysis is conducted using ICP-MS, described in Part 3, with lead levels normalized to calcium in order to control for variation in mineral content between samples.

Marginal Cost: Not reported.

Personnel Requirements: Significant expertise required for analysis.

Equipment Requirements: Significant equipment needed for sample preparation and analysis.

Logistical Requirements: As analysis is carried out on teeth which have fallen out, these may be sent to a central location for analysis; there is no need for sampling to be conducted in a clinical setting.

Precision and Limit of Detection: Not reported.

Risk of Contamination: Risk is significantly less than for Surface Dental Enamel Acid Etch Microbiopsy, but care must be taken.

Timeliness of Results: Not reported.

Ethics and Acceptability: Teeth must be extracted or fall out naturally. Extraction for the sole purpose of measurement is not ethically viable. In some cases, researchers may be able to acquire teeth that have been extracted for other health-related purposes, or which have fallen out due to natural causes (including baby teeth). However, researchers must still be careful to ensure that individuals or caregivers offer informed consent for their samples to be used, and that the data collection effort does not inadvertently incentivize or coerce forcible extraction. Any data collection approach should be reviewed and approved by an ethics board.

Part 5: Portfolio analysis and priorities for innovation

Previous sections describe the characteristics of individual measurement methods for lead exposure, including strengths and limitations across selected performance criteria. This section evaluates the performance of the entire *portfolio* of measurement approaches relative to different use cases for which they might be needed, with a focus on the requirements of LMIC settings. We consider the strengths and weaknesses of the full portfolio; evaluate the portfolio's performance for each of the five use cases of lead exposure measurement described in Part 1; and present a forward-looking agenda for research and development to address the most relevant gaps in the toolkit vis-à-vis the needs of LMIC policymakers, clinicians, and researchers.

Portfolio analysis: strengths

In considering the portfolio of testing tools, we observe the following strengths:

High-Accuracy "Gold Standard" Laboratory Methods: Existing "gold standard" laboratory-based methods for BLL testing, in contexts where laboratory analysis and expertise are available, offer highly precise and accurate measurements of blood lead at relatively low marginal cost. In high-resource countries like the United States, it is feasible and affordable to conduct laboratory-based BLL testing on a routine basis, including for universal screening of children.

Validity of Capillary Blood Draws: While imperfect, there are now several different well-validated methods for BLL testing using capillary blood draws, which are more acceptable to patients and caregivers than venous blood draws, and which can be collected by technicians with less specialized training.

Strong Biomarkers for Long-Term Exposure: The physical properties of both bone and teeth are well-suited to use as biomarkers of long-term exposure, and can be used, at least in theory, to document a highly accurate timeline of exposure over an individual's life course.

Availability of a Point of Care System: Point of care BLL testing is available using LeadCare II, and the device cost is reasonable ($3,000) for HIC primary care providers and LMIC hospitals/higher-level care facilities. This also suggests proof of concept for the overall technical feasibility of POC testing, which should in theory be duplicable by other manufacturers/innovators.

Portfolio analysis: limitations

In considering the portfolio of testing tools, we observe the following limitations:

High Dependence on Laboratory Capacity and Trained Personnel: Almost all testing approaches require highly trained personnel for sample collection and/or analysis, as well as access to sophisticated laboratory equipment, which are rarely available at the requisite scale in LMIC contexts. We specifically note the following gaps in the portfolio of testing methods:

- ***Lack of Equipment-Free BLL Testing Options:*** All BLL testing options require some type of fixed equipment/capital investment; there are no single-use, disposable, self-contained screening tests that can be widely deployed for self-testing, or for testing in non-clinical contexts. (Many similar tests exist for other conditions/health concerns and are widely available at very low cost in LMIC contexts, including pregnancy tests, HIV self-tests, malaria rapid diagnostic tests, and COVID-19 tests.) In practice, this limits BLL testing to contexts with extensive laboratory capabilities, or with acquisition of dedicated LeadCare II devices.

- ***Limited and Sub-Optimal Options for Point of Care BLL Testing:*** Point of care testing is highly desirable in resource-limited contexts, as it bypasses the need for extensive laboratory expertise and equipment while also offering immediate results for patient, allowing for prompt diagnosis and clinically appropriate care. Currently, the LeadCare II system is the only option available for point of care BLL testing. While LeadCare II can be deployed at lower-level health facilities and may be useful as a screening tool, it has several downsides; these include up-front equipment costs ($3,000 per device), relatively high marginal costs of test kits ($10 each), a high limit of detection, low precision, short shelf-life, cross-contamination associated with the finger prick, and operational constraints that prohibit use in very hot climates or at high elevation, as well as environments at high risk for contamination. The high marginal cost of the test kits is a particularly important barrier for LMICs, and is likely to make LeadCare II unaffordable as a screening tool in most LMIC contexts (especially given the need for subsequent confirmatory testing).

Limited Affordable Testing Options for LMIC Contexts: BLL testing options are generally affordable in HIC contexts, but are too costly for widespread routine use in most LMICs. However, existing testing approaches may be cost-effective for relatively limited applications in highly at-risk populations or among small population samples.

Immature Methods to Assess Long Term Lead Exposure: While biomarkers of long-term lead exposure (bone and teeth) are well-accepted in theory, methods for their actual use/deployment are still relatively immature and used primarily in experimental research and/or validation studies. Further validation and acceptance is required before they are widely accepted for mainstream use, including as an input to most research on the causes and effects of human lead exposure.

Difficulty Distinguishing Short- and Long-Term Lead Exposure in Chronically Exposed Populations: While BLL is generally used as a biomarker of short-term exposure to lead, its validity in this respect is compromised in chronically exposed populations; such populations may exhibit persistently elevated BLLs for many months or years after short-term exposure has ceased because lead is remobilized from storage in bone in certain circumstances. There is no obvious way to correct or account for this effect (except in the youngest children), and therefore no way to confirm in the medium-term whether persistently high BLLs in most individuals reflect ongoing exposure or an artifact of long-term exposure.[xcvii]

Portfolio analysis: performance for LMIC use cases

In this section, we briefly offer a qualitative assessment of the performance of the overall portfolio of testing option against the use cases for lead exposure measurement outlined in Part 1:

Clinical management of lead poisoning: moderate to poor

Available testing options are not broadly fit for purpose for the diagnosis and clinical management of lead poisoning in LMIC contexts, as they are too demanding of trained personnel and equipment, and/or too costly, to be integrated into most LMIC primary healthcare systems. However, testing options may be sufficient for severely ill patients who are undergoing diagnosis and treatment at hospitals or other higher-level facilities; it is feasible that many hospitals in LMIC settings could be equipped with LeadCare II devices or able to leverage in-house or nearby laboratory capabilities, and the marginal cost of testing would likely be cost-effective in most settings given high severity of a patient's condition.

Screening for elevated blood lead levels: poor

There are no BLL testing methods which are sufficiently low-cost and acceptable to enable at-scale use in screening programs at the population level in most LMICs, with the potential exception of some wealthier upper middle-income countries, e.g. Mexico. However, available options may be sufficient for screening of very high-risk populations with elevated prevalence of severe lead poisoning, e.g. populations that are occupationally exposed to lead or in close proximity to contaminated sites.

Monitoring and surveillance: moderate to poor

It is possible to conduct active surveillance exercises, e.g. nationally representative BLL surveys, at reasonable cost, given that only a relatively small subset of the population must be sampled and tested to yield representative results. However, as existing methods are too onerous and/or costly to integrate into routine screening, passive surveillance is not easily facilitated in LMICs using the exiting toolkit. Costliness and logistical constraints may also limit the frequency and sample size with which BLL monitoring exercises are conducted, limiting ability to discern subnational patterns or track progress/trends using an active surveillance approach.

Research: moderate

Even in LMIC settings where laboratory capabilities are lacking, researchers can generally access and afford gold-standard BLL testing (venous blood draws and laboratory analysis) for highly accurate and precise BLL measurement, potentially through international shipping of samples to foreign laboratories for analysis. However, methods for measuring long-term exposure—which are most relevant for research purposes—are still immature, and not necessarily immediately deployable in LMIC field settings. Relatedly, existing methods may struggle to distinguish short-term from long-term exposure in chronically exposed populations, which are common in LMICs. This challenge is highly relevant for some forms of research, for example to evaluate the effectiveness of interventions to reduce human lead exposure; if BLLs remain elevated even when short-term exposure has been stopped or eliminated, it is difficult to know whether an Intervention

has been effective simply by measuring BLL over a short-term time horizon (i.e., if BLL are being impacted from remobilized lead from the bones).

Establishing liability: moderate to strong

As with research, investigators or potential plaintiffs should in most cases be able to access gold-standard laboratory testing of BLLs, even if doing so requires international analysis of samples. However, some methods for measuring long-term exposure are still immature and not fully validated, which may limit their acceptability in legal settings.

Priorities for research and development

With a view to the gaps in the existing portfolio of measurement tools and their programmatic implications, we suggest the following priorities for a research and development agenda:

- **Very Low-Cost Equipment-Free Screening Tests:** Given the fiscal and capacity constraints in LMIC contexts, very low-cost, equipment-free screening tests—analogous to self-tests for malaria, pregnancy, or COVID-19—could be transformative for screening, diagnosis, and clinical management. It is unlikely that such a test could produce a precise BLL measurement, and any test using a capillary measure would be at some risk for contamination; follow-up venous testing might still be required to confirm severely elevated BLL results. Nevertheless, there are several potential approaches that would nonetheless offer high practical utility:

    - ***Screening test with a binary outcome:*** This form factor would indicate whether BLLs were above or below some pre-specified level with clinical or policy relevance; for example, a test could be "positive" at all BLLs above 5 µg/dL, and negative at all levels below that reference level. Such a test would allow healthcare providers to quickly assess whether a child is likely to have an elevated BLL and offer appropriate follow-up, for example more precise confirmatory testing; lead exposure prevention education; and potentially calcium and iron supplementation. Similarly, such tests could be offered to a group of individuals in a non-clinical setting, e.g. to a classroom or workplace, to quickly and cheaply assess the prevalence of elevated BLLs above the indicated threshold. Ideally, tests would be available with multiple "thresholds" of different relevance to different populations.

    - ***Screening test with indicative ranges:*** Using a capillary blood sample, this form factor would report an indicative range using a colour spectrum (e.g., as with ketone urine dipsticks) or darkening gradient (e.g., as with pregnancy tests that darken progressively as HCG levels rise). These tests would not be useable as a monitoring or research tool, as they cannot report precise results, but could nevertheless be quite useful for clinical triage and population screening, as they would roughly indicate an individual's BLL range, which could then imply different follow-up measures.

- **Marginal Improvements to LeadCare II Form Factor:** The LeadCare II form factor has many useful fundamentals, including low equipment cost; limited required expertise; and point-of-care, rapid reporting of results. However, marginal improvements are needed to make the system broadly fit-for-purpose in LMIC settings. These include much lower cost and longer shelf-life of test kits, as well as useability in hot climates and at elevation. In addition, the usefulness of LeadCare II is currently limited by its relatively low precision and high limit of detection, which in most cases precludes its use for precise estimation of population-level BLLs, or within other research; it also means that most clinical decision-making requires follow-up confirmatory testing with more precise laboratory methods. Higher precision would make a LeadCare II-like device more relevant across a broader range of BLL measurement use cases.

- **Validation of XRF for Dried Blood Spots:** Sampling with dried blood spots offers many practical advantages: doing so allows for capillary vs. venous blood draws; obviates the need for refrigerated transport of samples; and allows for tests to be processed at very low marginal cost, and potentially in a field setting (if a portable device is used). These properties can make this method very attractive for screening and monitoring use cases. However, there is still low acceptance of this method among experts. Additional validation is needed to mainstream XRF testing of dried blood spots as a widely accepted method for routine BLL testing.

- **Further Validation and Documentation of Bone and Teeth Testing:** Methods for measuring lead in bone and teeth appear technically sound to indicate long-term/cumulative lead exposure, but they are still not widely accepted by practitioners or fully documented in the public domain. Additional studies would be helpful to provide detailed documentation of the protocols for conducting these methods; further validate their performance/application for different research questions; provide reference values that relate lead concentrations in bone and blood to clinical significance/corresponding blood lead levels over the life course; and demonstrate practical applications for public health or social science research.

Conclusion

A perennial obstacle to addressing lead poisoning is its invisibility; more local data demonstrating the extent, severity, and distribution of lead exposure in more populations is urgently needed to spur policymakers into action. And in fighting lead poisoning, the ability to measure lead exposure—triangulated with other data sources, including lead concentrations in consumer goods, food, water, and environmental media—is indispensable in understanding where action is most urgently needed, which sources of exposure should be prioritised, and which actions are most effective.

This paper has reviewed the state of science on methods to measure lead exposure in humans, with the aim of informing policymakers and other non-technical audiences about the options for data collection and diagnosis. The five different use cases outlined in Part 1 each demand a unique profile in the tool(s) they employ to measure lead exposure. We find that there are a surprisingly large range of measurement tools available, many of which have attractive features for at least some use cases. However, when applied to LMIC contexts, the existing suite of methods does not offer fit-for-purpose tools for many essential applications, including front-line clinical management, population-level screening, and routine monitoring. Further, many attractive options for measuring long-term lead exposure are not fully validated and/or widely accepted, limiting their application outside of experimental studies.

Our findings indicate that funders of lead poisoning prevention and mitigation should consider investments in research and development, alongside investments in country level testing, surveillance, and response capacity, to facilitate broader scale up of effective lead control programs across LMIC contexts. Specific recommendations for priority R&D focus areas are presented in part 5. Further investigation is required to better understand the practical barriers to development of improved diagnostic tools, especially for BLL testing; these may include technical challenges or lack of perceived market opportunity, among others. Depending on the exact shape of the problem, funders may have an opportunity to catalyse market-based R&D with targeted investments or guarantees, for example with prizes or advanced market commitments for improved testing approaches (e.g., the CDC's Lead Detect Prize[9]), potentially combined with efforts to increase manufacturer engagement in lead testing, e.g. targeted outreach to India's large and sophisticated diagnostics industry. In addition, there may be high-leverage opportunities to expand testing options by further validating technologies that already exist and appear promising, but which have not yet received mainstream acceptance, for example use of XRF with dried blood samples. Given increasing funder and policy interest in addressing global lead poisoning, we encourage funders to consider robust investments in this area.

9 See more at https://www.leaddetectprize.com/.

Annex: Roundtable agenda

Methods to Measure Lead Exposure

Technical Roundtable

TUESDAY JANUARY 16, 2024

3PM—6PM GMT

Background

The capacity to measure lead exposure in an accurate, safe, and affordable way underpins any potential research or indeed action agenda on lead poisoning. There remains a dearth of data on population exposure levels in most low and middle-income countries (LMICs). This knowledge gap means we don't know just how big a problem lead poisoning in LMICs is, where it is most severe, and what progress is being made. Population surveys in Georgia, and more recently, India, have spurred policymakers into action against lead poisoning, demonstrating the persuasive power of exposure data relative to imputations, which are for most countries the only estimates presently available. In the long-term, a robust health sector should work towards a surveillance system with routine exposure monitoring, to identify hotspots and surges in exposure.

But large-scale testing is constrained by the prohibitive marginal costs and laboratory capacity demanded by the established method for measuring exposure, which involves a venous blood draw followed by testing by a phlebotomist. Scaling up measurement will likely require the implementation of one of several less cost-intensive methods for measuring blood lead levels, which are still relatively unproven at scale.

In parallel, research into the effects of lead poisoning requires measuring not only present, but long-term, or even lifelong exposure. Several methods have been shown to approximate this, but there remain questions about their precision and feasibility.

Objectives

As part of a broader body of work defining a priority research agenda to inform efforts against lead poisoning, the Center for Global Development is convening a half-day technical roundtable on methods for measuring lead exposure. The sessions will explore the measurement of both present and long-term exposure, and will consider the merits and drawbacks of both established and more experimental methods.

Objectives of the roundtable are as follows:

- To take stock of the state-of-the-science on lead exposure measurement, including the advantages and disadvantages of different methods;
- To clarify areas of uncertainty with respect to the accuracy and precision of different methods, and inform a research agenda for further validation/calibration where necessary/useful; and
- To consider the technical feasibility (in principle) of emerging and alternative measurement approaches, including directions for future research and development into novel testing methods.

Following the roundtable, and informed by its discussions, CGD intends to publish a short policy note summarising these issues.

Participant list

Name	Title and Affiliation
Rachel Silverman Bonnifield	Senior Policy Fellow, Global Health Policy, Center for Global Development (CGD)
Anouk Amzel	Medical Officer, U.S. Agency for International Development (USAID)
Ana Navas Acien	Professor, Department of Environmental Health Sciences, Columbia Mailman School of Public Health
Malia Boggs	Senior Technical Adviser for Child Health, Office of Maternal, Child Health & Nutrition, USAID
Sara Brosche	Science Advisor, International Pollutants Elimination Network
Jack Caravanos	Clinical Professor of Global Environmental Public Health, School of Public Health, New York University (NYU)
Lilian Corra	Senior Advisor, Global Alliance on Health and Pollution
Lee Crawfurd	Research Fellow, Education, CGD
Mark Engman	Director of Policy and Advocacy, Pure Earth
Bret Ericson	Consultant, UNICEF
Julius Fobil	Chair, Department of Biological, Environmental and Occupational Health University of Ghana School of Public Health
Cameron Fox	Senior Associate, Luminary Labs
Apala Guhathakurta	Public Health, Bloomberg Philanthropies
Santosh Harish	Program Officer, Global Public Health Policy, Open Philanthropy
Jessica Harrison Fullerton	Global Development Incubator
Paromita Hore	Director, Environmental Exposure Assessment and Education, NYC Department of Health and Mental Hygienee
Howard Hu	Flora L. Thornton Chair of the Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California
Gabriel Sanchez Ibarra	Vice President, Programs, Pure Earth
Jeff Jarrett	Research Chemist, Centers for Disease Control and Prevention
Daniel Kass	Senior Vice President, Environmental Health, Vital Strategies
Jessica Leighton	Public Health, Bloomberg Philanthropies
Karen Levy	Co-Founder, Fit for Purpose
Maria Paola Lia	Executive Director, Global Alliance on Health and Pollution
Drew McCartor	Executive Director, Pure Earth
Desiree Raquel Narvaez	Environmental Health Specialist, UNICEF
Emily Nash	Technical Advisor, Pure Earth
Ana Navas-Acien	Professor and Vice-Chair of Research, Environmental Health Sciences, Columbia Mailman School of Public Health
Anne Nigra	Professor, Environmental Health Sciences, Columbia Mailman School of Public Health
Lucile Okio	Senior Program Manager, Global Alliance on Health and Pollution
Kelly Olympio (By Recorded Rresentation)	Professor, Department of Environmental Health, University of São Paulo
Lesley Onyon	Unit Head for Chemical, Safety and Health World Health Organization (WHO)
Bo Pedersen	Regional Survey Coordinator, UNICEF

(Continued)

Name	Title and Affiliation
Ben Savonen	Senior Associate, Global Development Incubator
Abheet Solomon	Global Programme Lead, Healthy Environments for Healthy Children, UNICEF
Aaron Specht	Assistant Professor, School of Health Sciences, Purdue University
Carthur Wan	Senior Associate, Luminary Labs
Valerie Zartarian	Senior Scientist and Advisor, Center for Public Health and Environmental Assessment (CPHEA), Office of Research and Development (ORD), US Environmental Protection Agency (EPA)

Agenda

3:00–3:10 GMT	**Welcome and Participant Introductions** *Facilitated by Rachel Silverman Bonnifield*
3.10–3.20 GMT	**Setting the Scene: Roundtable Motivation and Process** *Facilitated by Rachel Silverman Bonnifield* Objectives: Summarise the issue of measuring lead exposure; set out aims of Roundtable.
3:20–4.10 GMT	**Measuring Present Exposure** *Presentations followed by group discussion* • *Fundamentals of Blood Lead Testing*—Professor Howard Hu, Flora L. Thornton Chair of the Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California • *Deep-dive on Venous and Capilliary Blood Testing*—Jeff Jarrett, Research Chemist, Centers for Disease Control and Prevention • *Brief Interjection on Potential for using XRF with Dried Blood Spots*—Aaron Specht, Assistant Professor, School of Health Sciences, Purdue University • *Testing in a Resource-Constrained Setting*—Abheet Solomon, Global Programme Lead, Healthy Environments for Healthy Children, UNICEF Objective: Build understanding around the state-of-the-science for measuring present exposure, and the considerations in applying available methods to measuring population exposure in low and middle-income countries. Consider further areas for innovation in measuring present exposure.
4:10–4.20 GMT	**Break**
4:20–5:10 GMT	**Measuring Long-Term Exposure** *Presentations followed by group discussion* • *Biomarkers of Long-Term Exposure*—Ana Navas Acien, Professor, Department of Environmental Health Sciences, Columbia Mailman School of Public Health • *Teeth as a Biomarker for Long-Term Exposure (Recorded Presentation)*—Kelly Olympio, Professor, Department of Environmental Health, University of São Paulo • *Using XRF to Measure Lead in Bone Tissue*—Aaron Specht, Assistant Professor, School of Health Sciences, Purdue University Objective: Build understanding about the current methods available for measuring long-term exposure. Consider further areas for innovation in measuring long-term exposure.
5.10–5.50 GMT	**Areas for Innovation in Measuring Exposure** *Presentations followed by group discussion* • *Current Needs For Exposure Measurement*—Emily Nash, Technical Advisor, Pure Earth • *Lead Detect Prize for Innovation in Measuring Exposure*—Cameron Fox, Senior Associate, Luminary Labs Objective: Consider potential areas for more experimental research in methods for measuring exposure.
5.55–6:00 GMT	**Wrap-Up** *Rachel Silverman Bonnifield*

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