UiT The Arctic University of Norway

The Georgian Lead Surveillance System (G-LESS)

A final report to the United Nations Children's Fund Georgia

June 29, 2022. Revised August 30, 2022.

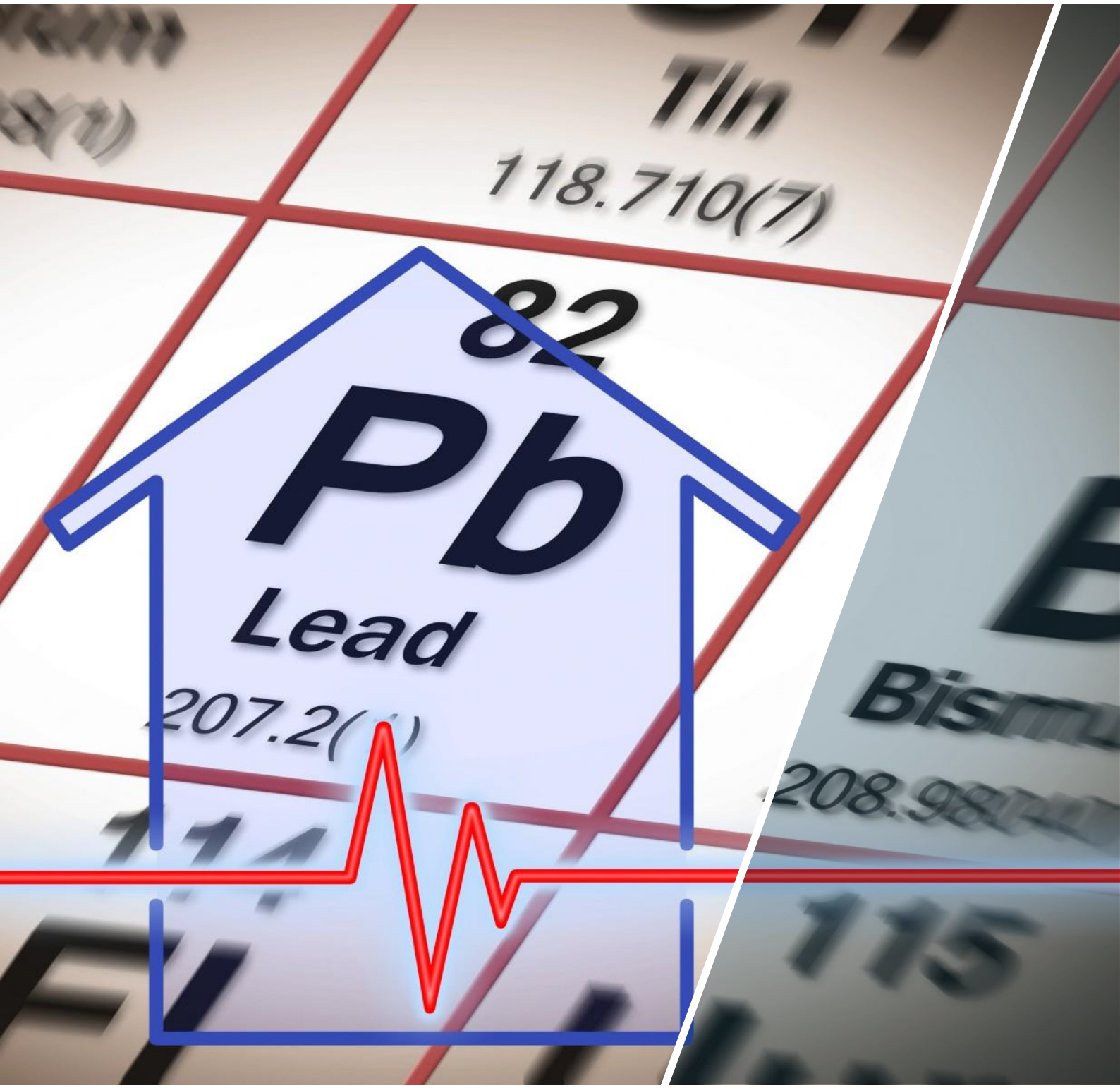

Illustration: mostphotos.com

Preface

In January 2022, the United Nations Children's Fund (UNICEF) Georgia released a tender with the following objective: *"Establishment of a National System for Environmental Health Surveillance in Georgia"*.

Among the deliverables were:

i. Description of the design of the surveillance system, including functional components and developmental steps to be taken.
ii. Operational implementation and delivery of standard methods of blood lead level testing, isotopic ratios and other chemical analysis of blood and environmental samples using the instrumentation available at the National Center for Disease Control and Public Health (NCDC) Chemical Risk Factor Research Laboratory.
iii. Data management and reporting systems.
iv. Medical management of individuals with high blood lead levels.
v. Procedures for identification of possible exposure sources, exposure sources investigation, impact mitigation or eradication, and Public Health preventive actions.

UiT the Arctic University of Tromsø (UiT) applied for this tender with the desire to contribute to the reduction of lead exposure in Georgian children. Results from the 2018 Multiple Indicators Cluster Survey (MICS) in Georgia indicate that the country faces severe public health challenges related to lead exposure, with 62% of children having blood lead levels ≥3.5 µg/dL. In order to get a better understanding of lead exposure in Georgia, it was important for us to personally assess the MICS datasets, and the background section of this report summarizes the main findings from that assessment.

The authors of the main body of this report are Professor Charlotta Rylander and Associate Professor Erik Eik Anda, from the Department of Community Medicine at UiT. Dr Rylander is an epidemiologist with extensive research experience regarding human health effects of environmental contaminants. Dr Rylander has collaborated in biomonitoring studies of pollutants, including toxic metals in Norway, Vietnam, South Africa, and Russia. She has been involved in research in Georgia since 2016, including quality control of the Georgian Birth

Registry (GBR), and is currently involved in several on-going research projects using data from national registries in Georgia. Dr Anda is an epidemiologist who has worked with surveillance systems, blood sampling, and blood analysis, including lead, in mothers and children in Bangladesh, Russia, Georgia, and Norway. The most recent project in Norway included collection and analysis of microvolume blood samples from 30,000 individuals. Dr Anda also has extensive knowledge of the Georgian health care system, including the GBR.

We would like to recognize the authors of the analytical and laboratory methods sections, who include Pierre Dumas and Ciprian Mihai Cirtiu from the Institut national de santé publique du Québec. Senior Chemist Dumas and Dr Cirtiu are experts in the development and implementation of methods for the detection of toxic metals in blood samples, including microvolume blood samples. Senior Scientist Hilde Uggerud and Senior Engineer Marit Vadset from the Norwegian Institute for Air Research have decades of experience with lead analysis and have implemented laboratory methods for lead detection in low- and middle-income countries. In addition, we greatly appreciate the input we received from the participants of the workshop in Tbilisi on May 25 and 26, 2022. We extend special thanks to Tinatin Manjavidze, Ana Aslanikashvili, Nia Khachidze, Vladimer Khasia, Tako Ugulava, Nino Dzotsenidze, Kari Wagelid Grønn, and Trudy Perdrix-Thoma for practical help.

Finally, we would like to emphasize that we endeavored to make an objective assessment of the situation and make the best recommendations possible to solve the problem of lead in Georgia, while tailoring our recommendations to Georgia's needs and its existing Health Management Information System, without any prior commitments or ties that might cause a conflict of interest, and taking into account only those requirements made by UNICEF Georgia when they selected us for this task. We would like to thank UNICEF Georgia for this opportunity, and we hope that, once implemented, our recommendations can help Georgia reach its goal of complete elimination of lead in its children.

Tromsø, June 29, 2022

Charlotta Rylander

Erik Eik Anda

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1 List of abbreviations

As – arsenic

BLLs - blood lead levels

Cd – cadmium

CDC - The United States Centers for Disease Control and Prevention

CI - confidence interval

CRF - chemical risk factor

Cu – copper

G-LESS - The Georgian Lead Surveillance System

GBR - Georgian Birth Registry

GEL - Georgian lari

Hg – mercury

HMIS - Health Management Information System

ICP-MS-MS - Inductive Coupled Plasma Mass Spectrometry Mass Spectrometry

INSPQ - Institut national de santé publique du Québec

IQ- intelligent quotient

LIRs - lead isotopic ratios

MICS - Multiple Indicators Cluster Survey

MMR vaccine- measles-mumps-rubella vaccine

Mn – manganese

MoHLSA - Ministry of Health, Labour, and Social Affairs of Georgia

NCDC - National Center for Disease Control and Public Health

OR – odds ratio

p – probability value

Pb – lead

ppm – parts per million

SHP - The State Health Program

SMS – short message service

SRM - standard reference material

t - t-statistics

UiT - UiT the Arctic University of Tromsø

UNICEF - the United Nations Children's Fund

VRS - Vital Registration System

WHO - World Health Organization

XRF - X-Ray Fluorescence

Zn – zinc

β- beta, a regression coefficient,

µg/dL – micro grams per deciliter

2 Executive summary

A country's ability to successfully implement a national surveillance system is dependent on the political and public will to do so. We believe that this will is strong in Georgia, which faces a large public health challenge related to lead (Pb) exposure in children.

The United States Centers for Disease Control and Prevention (CDC) has cited blood lead levels (BLLs) ≥3.5 µg/dL as the level of concern; BLLs ≥5 µg/dL are considered to cause developmental and neurological problems. According to the 2018 Multiple Indicators Cluster Survey (MICS), 62% of Georgian children have BLLs ≥3.5 µg/dL and 45% have BLLs ≥5 µg/dL. These proportions are even higher in Western Georgia, especially in Adjara, where 92% of children have BLLs ≥3.5 µg/dL and 87% have BLLs ≥5 µg/dL. Analysis of MICS data showed that living in a rural area of Adjara or coming from a poor family increased the risk of high BLLs even further. In real numbers, the proportions of BLLs ≥3.5 µg/dL and ≥5 µg/dL reported in the MICS (62% and 45%) translate to 248,000 children aged 1 to 8 years in Georgia with BLLs over the level of concern, of which 180,000 have BLLs that may cause irreversible health problems. New births add another several thousand children to these numbers every year. In addition, BLLs ≥5 µg/dL may cause a child to lose up to 6 IQ points*; at the proportions cited and with 50,000 births per year, Georgia is losing an estimated 135,000 IQ points annually. No country can afford that. Moreover, recent science supports the notion that there is no safe threshold level for lead in children – any level may cause harm. The only way forward is to implement primary prevention of lead exposure, with the long-term goal of eliminating lead exposure in Georgia. This can only be achieved through the removal of lead exposure sources, and ultimately, the removal of lead from the environment.

The State Health Program (SHP) offers a multitude of services to the residents of Georgia; it covers all free medical services in the country, e.g., antenatal care, immunizations, and BLL testing through the SHP for Lead Biomonitoring. This biomonitoring component of the SHP represents secondary prevention: identifying symptomatic children with suspected high BLLs, screening them for BLLs, and then treating them if necessary. This would be beneficial if the identification process and the available treatment were effective. Unfortunately, scientific reports have revealed the near impossibility of effectively identifying children with high BLLs using questionnaires and doctor's recommendations alone, and these same reports show that

*Lanphear BP, Lowry JA, Ahdoot S, Baum CR, Bernstein AS, Bole A, et al. Prevention of childhood lead toxicity. Pediatrics. 2016;138(1).

the effectiveness of treatment for high BLLs is doubtful at best when lead exposure sources are not removed. However, the SHP for Lead Biomonitoring did implement one public health primary prevention measure that should not be ignored: they introduced lead biomonitoring and informed the public about it, meaning that more people became aware of the issue of lead exposure in children.

In this report, we propose the creation of a Georgian Lead Surveillance System (G-LESS), formerly referred to as the Georgian Integrated Surveillance System for Lead. This national, uniform system will reveal more lead exposure sources, monitor the effect of removal of lead exposure sources on a national and regional level, sustainably measure BLLs and lead levels in environmental samples in Georgia at its National Center for Disease Control and Public Health (NCDC) Chemical Risk Factor (CRF) Research Laboratory, and follow-up children who have high BLLs.

The G-LESS will be structured to take advantage of the existing, successful SHP for Immunizations, as most children in Georgia follow the recommended immunization schedule, and all participants in the SHP for Immunizations have their information recorded in the Immunization Module of Georgia's Health Information Management System. Thus, to simplify and optimize the recruitment of children, BLL screening, results, and follow-up, we suggest adding a Lead Module to the existing Immunization Module and link information from the Georgian Birth Registry (GBR) and the Vital Registration System (VRS). We recommend monitoring children, not mothers, as lead exposure is on-going, and changes in exposure will be easier to detect in children than in adults.

The G-LESS would require an estimated 3 years of development, testing, and implementation before it is fully operational. During this period, we suggest to simultaneously identify (or exclude) as many potential lead exposure sources as possible using lead isotopic ratios (LIRs) in the blood of children and in environmental samples from their immediate surroundings. Historically, acquiring venous blood samples from children has been difficult, and it was often uncomfortable for the children. Therefore, instead of venous blood samples, the G-LESS calls for the use of microvolume blood samples, which are collected using a volumetric absorptive microsampling device, or microsampler, that only requires 2 x 20 µL of blood (or 2 drops). The technique fixates the blood sample, making it unable to interact with the

surrounding environment, and the sample has a known volume, which allows for quantitative measurements. The resultant microvolume blood samples are also easy to transport and can be stored for several months at room temperature. We detail analytical methods in this report that will allow the NCDC CRF Research Laboratory to use cutting-edge methodology to determine not only BLLs, but also LIRs in the same microvolume blood samples.

Main recommendations:

1. Primary prevention of lead exposure in Georgian children is strongly recommended. This includes removing lead exposure sources and monitoring changes in BLLs over time.
2. A national, uniform system for revealing lead exposure sources is required. This includes increased BLL screening and LIR determination in exposed children and environmental samples from their immediate surroundings.
3. Changes in legislation that will facilitate prohibition of sale of certain types of consumer goods with high lead levels.
4. The current SHP for Lead Biomonitoring should be phased out and replaced by the G-LESS within 3 years.
5. The G-LESS must include a Lead Module; a digital system integrated into the Immunization Module used in the SHP for Immunizations.
6. To measure the effects of primary prevention, the G-LESS should recruit and analyze microvolume blood samples from a random sample of 4303 children annually.
7. The NCDC CRF Research Laboratory should focus on three components only, in order to develop accurate and efficient methods: i) lead analyses in microvolume blood samples, ii) lead analyses in environmental samples, and iii) LIR determinations in i) and ii).
8. Information and responsibilities related to lead exposure are fragmented in Georgia. The recommendation of this report is to establish a National Expert Group (including international experts) with full authority to manage the G-LESS, and that interacts directly with the NCDC CRF Research Laboratory and the Ministry of Health, Labour and Social affairs of Georgia.

3 Background

3.1 Lead in Georgia – The Multiple Indicators Cluster Survey

Publicly available data on blood lead levels (BLLs) in Georgia is limited, although the Multiple Indicators Cluster Survey (MICS) dataset is impressive. It contains data on BLLs in randomly selected children aged 2 to 7 years, but no information on maternal BLLs. We downloaded different datasets from the MICS website, and merged them according to household number, cluster number, and the specific study identification number assigned to each child. The available datasets contain information from 1520 children. As with most contaminant data, the BLL distribution is right-skewed. Therefore, median and minimum/maximum concentrations are reported as measures of central tendency in the included tables. BLLs of concern are defined as per the United States Centers for Disease Control and Prevention (CDC) (≥3.5 µg/dL, corresponding to the 97.5 percentile of BLLs in children from the United States general population) (1); BLLs ≥5 µg/dL are considered the threshold for developmental and neurological problems, and other adverse health effects in children, including attention deficit disorders, behavioral problems, and decreased cognitive performance (2). In the analyses below, we used the higher value of ≥10 µg/dL, because it is easier to find comparable references using this value.

3.1.1 BLLs according to region of residence and rural/urban area

Adjara, Guria, Imereti, and Samegrelo-Zemo Svaneti were the regions where the most lead contamination was found, with children in Adjara experiencing the highest median BBLs (Figure 1 and Table 1).

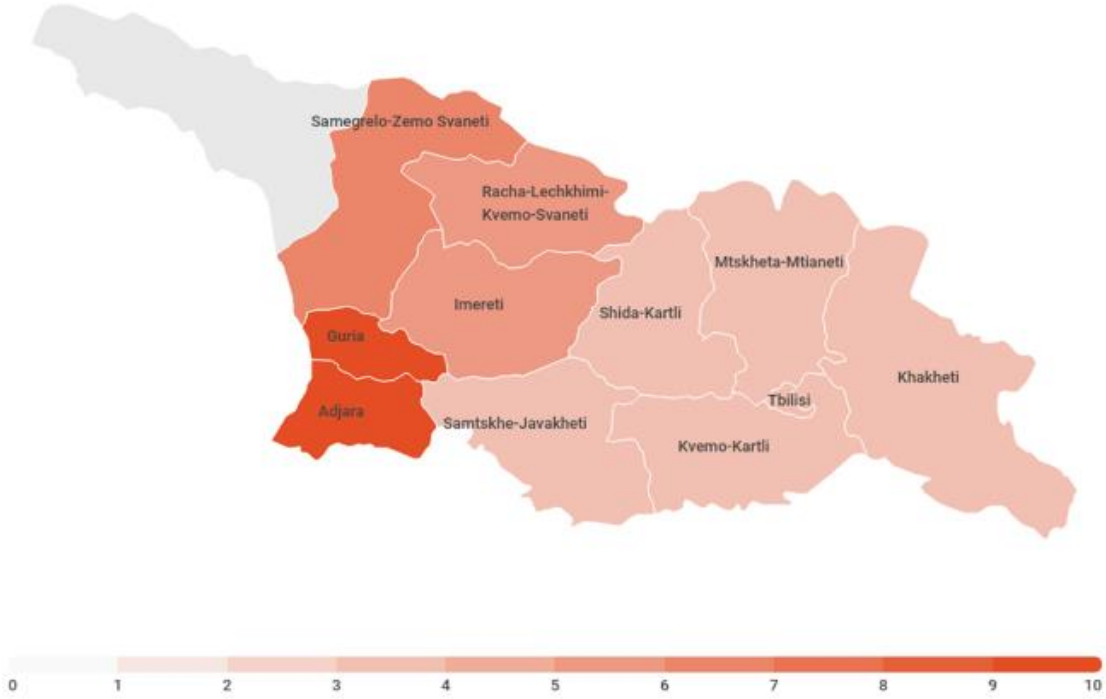

Figure 1. Median blood lead levels (µg/dL) according to region of residence. Multiple Indicators Cluster Survey, 2018.

The MICS dataset showed that 62% of children in Georgia had BLLs ≥3.5 µg/dL and 19% had BLLs ≥10.0 µg/dL. In Adjara, 92% of children had BLLs ≥3.5 µg/dL and 46% had BLLs ≥10.0 µg/dL. In the whole country, there was no difference in median or mean BLLs in rural/urban areas (Wilcoxon rank sum test: p=0.99, t-test: p=0.46). However, children residing in rural Adjara had significantly higher mean BLLs (61% with BLLs ≥10 µg/dL) than children in urban Adjara (t-test: p<0.01). No other regions showed this rural-urban difference in BLLs.

Table 1. Blood lead levels (BLLs) in children aged 2 to 7 years according to region of residence and rural/urban area. Multiple Indicators Cluster Survey, 2018.

Region			BLL (ug/dl)	BLL ≥3.5 ug/dL (%)	BLL ≥5 ug/dL (%)	BLL ≥10 ug/dL (%)	Region			BLL (ug/dL)	BLL ≥3.5 ug/dL (%)	BLL ≥5 ug/dL (%)	BLL ≥10 ug/dL (%)
		n	median (min-max)						n	median (min-max)			
Georgia	Total	1520	4.5 (0.68-51.9)	62	45	19	Mtskheta-Mtuaneti	Total	151	3.0 (0.8-29.1)	40	17	5
	Urban	678	4.6 (0.68-51.9)	63	46	18		Urban	12	3.7 (1.3-8.0)	58	25	0
	Rural	842	4.4 (0.78-39.7)	61	44	20		Rural	139	2.9 (0.8-29.1)	38	16	6
Tbilisi	Total	153	3.1 (0.68-36.7)	43	28	9	Samegrelo-Zemo Svaneti	Total	199	6.9 (1.0-29.6)	82	67	29
	Urban	143	3.0 (0.68-19.8)	41	27	8		Urban	122	7.1 (1.0-24.3)	79	66	34
	Rural	10	4.3 (1.6-36.7)	70	40	20		Rural	77	6.6 (1.8-29.6)	87	69	22
Adjara	Total	164	9.5 (1.1-41.3)	92	87	46	Samtskhe-Javakheti	Total	98	3.7 (0.95-21.9)	54	30	12
	Urban	90	7.9 (1.1-41.3)	88	81	34		Urban	25	4.2 (1.1-12.0)	72	28	4
	Rural	74	12.1 (1.1-39.7)	96	93	61		Rural	73	3.2 (0.95-21.9)	48	30	15
Guria	Total	152	9.3 (1.4-33.9)	89	74	43	Kvemo Kartli	Total	105	3.2 (1.1-18.9)	42	19	6
	Urban	30	7.6 (1.5-30.5)	80	60	33		Urban	46	3.2 (1.2-18.9)	37	17	4
	Rural	122	9.6 (0.98-33.9)	91	78	45		Rural	59	3.2 (1.1-18.6)	46	20	7
Imereti	Total	160	5.6 (1.0-51.9)	78	58	22	Shida Kartli	Total	207	3.1 (0.73-41.7)	42	24	4
	Urban	92	5.5 (1.3-51.9)	77	55	20		Urban	80	3.3 (0.74-41.7)	45	26	5
	Rural	68	6.0 (1.0-34.9)	78	60	25		Rural	127	3.0 (1.2-12.8)	40	22	4
Khakheti	Total	131	3.1 (0.8-16.1)	43	25	3							
	Urban	38	3.2 (0.8-14.2)	47	24	5							
	Rural	93	3.1 (1.2-16.1)	41	26	2							

min: minimum, max: maximum

3.1.2 BLLs according to age

Table 2 displays median (minimum - maximum) BLLs according to the age of the children when they were tested in the MICS. Overall, 6- and 7-year-olds had higher BLLs than 2-years-olds (linear regression: $p<0.05$). This trend persisted after adjusting for regional differences. There were no significant differences in BLLs according to age on a regional level, which might be due to smaller sample sizes. The fact that BLLs increase with age is likely an indication of on-going environmental exposure.

Table 2. Blood lead levels (BLLs) according to children's age and region of residence. Multiple Indicators Cluster Survey, 2018.

	Median BLL, ug/dl (min-max)					
Age	**2**	**3**	**4**	**5**	**6**	**7**
Georgia	4.0 (0.68-41.7)	4.5 (0.7-30.7)	4.5 (0.8-36.7)	4.2 (0.8-32.0)	4.7 (0.9-51.9)	4.6 (1.2-41.3)
Tbilisi	2.6 (0.68-8.7)	2.9 (1.1-18.0)	3.0 (1.1-36.7)	3.2 (0.9-11.9)	3.0 (0.9-15.7)	4.5 (1.4-19.8)
Adjara	8.0 (1.1-33.6)	9.1 (1.6-25.2)	9.8 (3.0-24.4)	8.9 (1.1-32.0)	11.5 (1.9-39.7)	13.1 (2.6-41.3)
Guria	8.6 (1.4-19.1)	8.5 (1.0-30.7)	10.5 (1.8-21.7)	9.5 (2.6-27.2)	9.6 (1.5-30.6)	7.6 (2.0-33.9)
Imereti	4.4 (1.3-18.1)	4.8 (1.0-22.5)	4.8 (2.1-17.9)	5.4 (1.6-28.6)	7.7 (2.7-51.9)	6.3 (1.8-34.9)
Khakheti	3.2 (1.3-10.6)	3.4 (1.7-8.5)	3.5 (1.2-7.3)	2.9 (0.8-7.5)	3.2 (1.3-16.1)	2.3 (1.2-9.1)
Mtskheta-Mtuaneti	3.5 (0.8-7.4)	3.8 (1.3-14.5)	3.3 (0.8-29.1)	2.4 (1.2-7.4)	2.7 (1.2-15.6)	2.6 (1.4-8.0)
Samegrelo-Zemo Svaneti	7.0 (2.1-26.8)	5.6 (1.5-24.3)	6.6 (1.3-28.0)	7.4 (2.4-21.8)	6.6 (1.0-20.1)	7.4 (2.0-29.6)
Samtskhe-Javakheti	2.8 (1.1-13.2)	4.3 (1.2-20.6)	3.3 (0.95-21.9)	3.3 (1.7-11.9)	4.6 (1.8-13.8)	3.5 (1.8-19.6)
Kvemo Kartli	3.2 (1.4-8.2)	2.8 (1.1-13.9)	3.5 (1.4-18.6)	3.0 (1.5-16.8)	4.0 (1.1-14.4)	3.6 (1.2-18.9)
Shida Kartli	2.6 (0.8-41.7)	2.5 (0.7-6.4)	3.4 (1.2-12.6)	2.9 (0.9-12.6)	3.2 (1.4-10.0)	3.9 (1.3-20.2)

min: minimum, max: maximum

3.1.3 BLLs according to sex and ethnicity

There were no differences in BLLs according to sex or ethnicity in Georgia as a whole, or in the most highly contaminated regions.

3.1.4 Drinking water, construction materials, and animals in the household

Not drinking water, exterior/interior wall and floor materials, nor presence of animals in the household were associated with BLLs (multivariable linear regression: $p>0.05$).

3.1.5 Wealth index

Children from the wealthiest households had significantly lower BLLs than children from less privileged households (Table 3, linear regression: p<0.05).

Table 3. Blood lead levels (BLLs) according to the wealth index of the family. Multiple Indicators Cluster Survey, 2018.

	Median BLL (min-max)	β (95% CI)	p
Richest	4.3 (0.68-28.6)	Ref.	
Fourth	6.6 (4.9-41.7)	0.39 (0.23,0.56)	<0.001
Middle	6.6 (0.74-51.9)	0.39 (0.24, 0.53)	<0.001
Second	6.8 (0.78-37.3)	0.43 (0.28, 0.58)	<0.001
Poorest	7.2 (0.84-39.7)	0.49 (0.34, 0.64)	<0.001

Note that BLLs were log-transformed in the regression model. β: regression coefficient from a simple linear regression, CI: confidence interval.

3.1.6 Predictors of elevated BLLs

Using multivariable linear regression analysis, we assessed predictors of elevated BLLs in the MICS dataset. After mutual adjustments, living in Adjara was the single most important variable; children aged 6 and 7 years had significantly higher BLLs than 2-year-olds, and BLLs increased with decreasing wealth index of the family (Table 4).

Table 4. Results of multivariable linear regression. All estimates are mutually adjusted. Blood lead levels were log-transformed. Multiple Indicators Cluster Survey, 2018.

Variable	β (95% CI)	t	p	Variable	β (95% CI)	t	p
Region				**Age**			
Tbilisi	Ref.			2	Ref.		
Adjara	0.92 (0.76, 1.07)	11.6	<0.001	3	0.06 (-0.06, 0.18)	0.97	0.33
Guria	0.70 (0.54, 0.87)	8.3	<0.001	4	0.09 (-0.03, 0.20)	1.4	0.15
Imereti	0.43 (0.27, 0.58)	5.3	<0.001	5	0.08 (-0.04, 0.20)	1.3	0.2
Khaketi	-0.21 (-0.38, -0.04)	-2.4	0.02	6	0.19 (0.07, 0.31)	3.2	0.001
Mtskheta	-0.25 (-0.41, -0.08)	-2.9	0.004	7	0.19 (0.07, 0.31)	3.2	0.001
Samegrelo-Zemo Svaneti	0.50 (0.34, 0.65)	6.3	<0.001	**Wealth index**			
Samtskhe-Javakheti	-0.03 (-0.34, 0.01)	-0.3	0.77	Richest	Ref.		
Kvemo Kartli	-0.16 (-0.34, 0.001)	-1.9	0.06	Fourth	0.23 (0.08, 0.38)	3.1	0.002
Shida Kartli	-0.20 (-0.35, -0.05)	-2.6	0.01	Middle	0.24 (0.10, 0.38)	3.4	0.001
				Second	0.30 (0.16, 0.44)	4.2	<0.001
				Poorest	0.38 (0.23, 0.52)	5.0	<0.001

β: regression coefficient, t: t-statistics, CI: confidence interval

Results from multivariable linear regression analysis of data from Adjara indicated that being from the poorest wealth index (β=0.88, t=2.89, p=0.004) was the most important predictor of elevated BLLs, followed by living in a rural area (β=0.30, t=2.07, p=0.04). Age was not associated with elevated BLLs in Adjara.

We also assessed the odds of BLLs ≥10 µg/dL with multivariable logistic regression analyses. The results were similar to those from the linear regression results. Compared to children living in Tbilisi, children in Adjara had 7.1 times higher odds of BLLs ≥10 µg/dL (odds ratio [OR]=7.12, 95% confidence interval [CI]: 3.57 - 14.2), children in Guria had 5.0 times higher odds (OR=5.04, 95% CI: 2.41 - 10.5), Imereti 2.2 times higher odds (OR=2.16, 95% CI: 1.04 - 4.47), and Samegrelo Zemo-Svaneti 2.9 times higher odds (OR=2.89, 95% CI: 1.41 - 5.92). Children aged 6 years had 2.3 times higher odds of BLLs ≥10 µg/dL compared to 2-year-olds (OR=2.31, 95% CI: 1.38 - 3.87) and children aged 7 years had 1.7 times higher odds of BLLs ≥10 µg/dL (OR=1.73, 95% CI: 1.03 - 2.94). Children in the poorest wealth index had 3.1 times higher odds of BLLs ≥10 µg/dL (OR=3.11, 95% CI: 1.40 - 6.93), those in the second poorest wealth index had 2.9 times higher odds (OR=2.89, 95% CI: 1.32 - 6.31), children in the middle wealth index had 2.3 times higher odds (OR=2.32, 95% CI: 1.07 - 4.99), and those in the fourth wealth index group had 2.3 times higher odds compared to the richest children (OR=2.33, 95% CI: 1.05 - 5.18). In Adjara, children in rural areas had 3.7 times higher odds of BLLs ≥10 µg/dL compared to children in urban areas (OR=3.66, 95% CI: 1.17 - 11.5).

3.1.7 Diet

Information about food intake was only given by mothers with children between 0 and 1 year of age, and these children were not included in the lead biomonitoring study of MICS. Thus, associations between diet and BLLs could not be addressed in the MICS dataset.

3.1.8 Toys

Information about types of toys were included in the questionnaires for children under 5 years of age. In the whole of Georgia, use of homemade toys was associated with elevated BLLs (linear regression: β=0.20, p=0.008), after adjustments for region of residence and wealth index. This is in line with Ericson et al, who found elevated lead levels in toys (3).

3.1.9 Breastfeeding

Only women with children aged 2 or younger responded to questions regarding breastfeeding (n=228). Ever breastfeeding the child (yes/no) was not associated with elevated BLLs after adjustment for region of residence, rural/urban area, wealth index, and use of homemade toys in the MICS.

3.1.10 Other toxic elements

In the MICS dataset, data on blood concentrations of mercury (Hg), manganese (Mn), arsenic (As), and cadmium (Cd) were also available. None of the mean/median concentrations were elevated, and there were no substantial differences across regions.

3.1.11 Summary of findings from the MICS

- Adjara has a high level of lead contamination. A considerable number of children in Guria, Samegrelo-Zemo Svaneti, and Imereti also experienced high BLLs. Although BLLs in the remaining regions are not as high, they are still elevated compared to many other countries.
- There is no difference in BLLs in rural/urban areas in Georgia, except in Adjara, where children in rural areas have elevated BLLs.
- BLLs increase with increasing age in children. This likely reflects on-going exposure.
- There are no differences in BLLs according to sex of the children.
- Drinking water and construction materials used in the home were not associated with high BLLs.
- BLLs increase with decreasing wealth of the family.
- Use of homemade toys is associated with elevated BLLs, also after accounting for region of residence, age, and wealth index.
- Associations between diet and BLLs could not be addressed due to lack of dietary data.
- Data on BLLs in mother-child pairs are lacking.

3.2 Other available studies of lead exposure in Georgia

The study by Avkopashvili (4) and co-authors from 2017 reported soil and water concentrations of toxic metals in mining districts in the Southwest and East-Central parts of Georgia. They concluded that Cu, Zn, and Cd deposits in soil are linked to mining activities. In addition, they reported maximum soil lead levels of 50 mg/kg in the Bolnisi district in Southeast Georgia. Since the authors only tested soil and water in selected areas, it is not possible to conclude whether the higher levels found in this study coincide with high BLLs found in children, but it is likely that at least some of the lead found in soil ends up in children.

In 2019, Hore et al (5) published a descriptive study on lead in spices from various countries, including Georgia. Between 2008 and 2017, they tested lead content in 1496 samples of more than 50 different spices, of which 31% had levels above the legal limit in the United States of 2 parts per million (ppm). The highest concentration was found in the Georgian spice “kviteli kvavili”, which measured at 48,000 ppm, and all the samples of this spice contained lead (mean: 240 ppm). Several other Georgian spices also contained lead levels above 2 ppm, whereas the samples bought and collected in the United States had consistently lower levels than the samples bought in Georgia. It is not clear from where the lead in these spices originated, but the authors mentioned that it could come from adulteration to add color or weight. It could also originate from the soils where the components were farmed. While speaking with different people in Georgia, the general perception seems to be that children do not eat spices, thus spices should not be an important source of lead exposure. However, it is likely that children eat much of the same foods as the adults in the same household.

In 2020, Ericson et al (3) published a descriptive study on the lead content of various environmental samples collected from homes and markets. The lead analyses were, for the most part, performed by portable X-Ray Fluorescence (XRF) measurements. The limit of detection for the equipment used was 8 mg/kg. In addition, they analyzed dust, water, and cookware (surface) by Atomic Absorption/Emission Spectrometry. Spices were found to have high lead levels, and homes in Adjara and Guria (Western Georgia) were much more likely to contain spices that measured above the reference level. It was not possible to establish a

significant, positive correlation between houses that contained contaminated spices and high BLLs in the children who lived there, due to the limited sample size. They concluded that the XRF can be a useful tool in the field assessment (screening) of spices. While they did report a high correlation between XRF measurements and other, more accurate methods, this only pertained to samples with concentrations higher than the XRF limit of detection. While the legal limit for lead content in spices is 2 ppm in the United States, it would be interesting to assess whether lead levels between 2 and 8 ppm in spices can cause seriously elevated BLLs in children.

Kazzi et al (6) published a short communication in 2020 that explained some of the historical reasoning behind including BLLs in Georgian children in the 2018 MICS. It also gave background information on blood sample collection in the MICS and reported some of its most important findings. They concluded that public health measures are important for decreasing lead exposure on a population level, which is in line with the general World Health Organization (WHO) recommendations to use primary prevention measures whenever possible (7).

The study by Ruadze and colleagues (8), published in 2021, is described as a longitudinal follow-up study of BLLs in Georgian children. Children with elevated BLLs in the MICS were eligible to participate in the State Health Program (SHP) for Lead Biomonitoring (described below), though not all who were eligible attended. The study followed attenders as they received health advice, calcium and iron supplements, multivitamins, and repeated BLL tests through this facet of the SHP. The main finding was that children who receive these interventions can reduce their BLLs over time. However, the authors could not report changes in BLLs during the same time period among children with elevated BLLs who did not participate in the SHP for Lead Biomonitoring.

There is an upcoming article by Leonardi and colleagues about lead isotopic ratios (LIRs) in children with high BLLs and in samples from their surrounding environment, however at the time this report was written, this article had not yet been published.

3.3 Benefits of treatment

Lead competes with calcium and iron for intestinal absorption (9). If iron and calcium intake is inadequate, intestinal lead absorption increases, thus calcium and iron supplements may reduce lead absorption. Chelating agents are pharmaceuticals (chelation treatment) that may also lower BLLs, as they bind to lead so that it can be excreted in the urine (10).

In 2019, a comprehensive review article (11) highlighted the global lack of research about the benefits and harms of BLL screening and of treating children and pregnant women with elevated BLLs. The review included results from previously published interventions studies from different parts of the world. None of the studies were from Georgia.

Among other issues, the comprehensive review found:

- Risk assessment instruments such as screening questionnaires performed poorly in identifying children with BLLs ≥10 µg/dL.
- Chelation treatment in children with BLLs ≥20 µg/dL decreased BLLs in the short-term, but BLLs reached levels similar to those in non-treated children some years after completing the treatment (11, 12).
- Chelation treatment did not improve neurodevelopmental outcomes. In fact, there were indications of harmful effects in treated children, such as shorter height and poorer scores on attention and executive function.
- No effects on BLLs in children were reported following residential lead hazard control techniques (education, home inspection, home cleaning kits, etc.).
- Poor-quality evidence that BLLs can be reduced by iron or calcium supplements in children. Calcium supplements reduced BLLs in pregnant women slightly; however only one study evaluated this, and it had certain limitations.
- No research on potential harms of screening for elevated BLLs in children.
- Limited research on the accuracy of screening questionnaires in pregnant women and no research on benefits or potential harms of BLL screening.

The 2021 WHO guidelines for the clinical management of lead exposure (7) support these conclusions, but recommend iron and calcium supplements in children and pregnant women with suspected deficiencies. Chelation treatment is only recommended in extreme exposure situations (BLLs ≥45 µg/dL) or as a lifesaving measure, although the strength of the evidence for these recommendations is low. In the MICS, there was only one child with BLLs ≥45 µg/dL.

4 Secondary prevention in the SHP for Lead Biomonitoring

Early detection of disease, for instance through screening programs, is defined as secondary prevention. The SHP offers a multitude of services to the residents of Georgia; it covers all free medical services in the country, e.g., antenatal care, immunizations, and also BLL testing through the SHP for Lead Biomonitoring, which is based on secondary prevention: identifying symptomatic children with suspected high BLLs, screening them for BLLs, and then treating them if necessary. The SHP for Lead Biomonitoring was initiated in 2019 as a response to the high BLLs found in children in the MICS. This SHP has an annual budget of 1,000,000 Georgian lari (GEL) and aims to prevent the harmful effects of lead, to diagnose high BLLs in a timely manner, and to manage cases with high BLLs. Children with indications of lead poisoning are referred to free BLL testing through the SHP for Lead Biomonitoring by their family doctor/pediatrician. The listed indications that warrant referral are many and non-specific and include, among others, abdominal pain, nausea, vomiting, irritability, and anorexia (13). Children with BLLs ≥5 ug/dL receive additional medical services from the SHP, and family members 18 years or older and pregnant family members are also invited for BLL testing. Additional medical services include repeated BLL testing at regular intervals, and free calcium and iron supplements prescribed by the family doctor/pediatrician. Children with BLLs ≥5 ug/dL also receive a consultation by a pediatrician, an evaluation of physical and psychological development based on a defined questionnaire, general information about lead exposure, and diagnostic tests such as blood count, ferritin, C-reactive proteins, blood iron level, hemoglobin or hematocrit, and abdominal ultrasound. In children with BLLs ≥10ug/dL, the National Center for Disease Control and Public Health (NCDC) also studies the child's home

environment, and the Ministry of Environmental Protection and Agriculture evaluates food and environmental risk factors such as air, water, and soil (13).

In 2020-2021, 14,182 children were referred to BLL testing through the SHP for Lead Biomonitoring. However only 1739 children (12.2%) had BLLs ≥10 µg/dL and four children (0.0003%) had BLLs ≥35 ug/dL (Communication with Ani Beraia, manager of the SHP for Lead Biomonitoring). This is in contrast to MICS results, which showed that 19% of children in Georgia had BLLs ≥10 µg/dL. The MICS contains a random sample of Georgian children, and thus will identify the proportion of children with BLLs ≥10 µg/dL more accurately than the referral system of the SHP for Lead Biomonitoring. The difference in the proportion of children with BLLs ≥10 µg/dL in the SHP and the MICS suggests that referral based on suspicions of lead poisoning does not efficiently identify children with high BLLs. Additionally, we do not know how many children with high BLLs are never referred to this facet of the SHP.

Moreover, the SHP for Lead Biomonitoring has so far been unable to identify and remove general lead exposure sources in Georgia. BLL results in individuals and families, and of exposure source investigations in the respective households, are not systematically collected in one database. As children are referred to BLL testing based on medical indications of vague symptoms that may stem from many different exposures and diseases, the children participating in the SHP for Lead Biomonitoring represent a highly selected group, thus it is possible that exposure source investigations from this group of children are also biased.

Still, the SHP for Lead Biomonitoring may well have raised awareness about the problem of lead exposure in Georgia. In which case, it is possible that the reduction in the proportion of children with BLLs ≥10 µg/dL observed in recent years in this facet of the SHP represents a real reduction. However, this cannot be confirmed without an unbiased surveillance system based on a random sample of participants.

The 2021 WHO guidelines for the clinical management of lead exposure, which are based on comprehensive systematic literature reviews, state that "*action should be taken to remove or terminate lead exposure*", and that all lead exposure is potentially preventable (7). Already in 2012, the United States CDC's Advisory Committee for Childhood Lead Poisoning Prevention concluded that primary prevention of lead exposure is necessary. The committee

argued that secondary prevention through treatment (as it is practiced in Georgia today) is no longer acceptable, as the effects of lead appear to be irreversible (14).

5 Primary prevention in the G-LESS

Primary prevention aims to prevent disease or injury before it occurs. Immunization programs are prime examples of primary prevention; indeed, numbers from the SHP for Immunizations in Georgia show that it is successful, as the vaccination coverage is relatively high and the incidence of vaccine-targeted illnesses is low. The proposed Georgian Lead Surveillance System (G-LESS) is based on a random sample of children. General exposure source investigations are part of the initial steps of the implementation of the G-LESS, with the aim of eliminating lead exposure for all children in Georgia. As described above, random sampling of children in the G-LESS will likely identify more children with elevated BLLs than the targeted approach of the SHP for Lead Biomonitoring. These children will be offered similar medical interventions as beneficiaries of the current SHP (Table 7), as well as individual exposure source investigations in line with the Georgian State protocol for the early detection and management of lead poisoning in children (13). The G-LESS aims to monitor the effectiveness of primary prevention efforts; at the same time, identified children with high BLLs will receive follow-up and treatment according to best practices. We show that the annual costs of the G-LESS will be less than those of the SHP for Lead Biomonitoring, thereby strengthening the argument to replace the SHP for Lead Biomonitoring with the G-LESS within 3 years.

5.1 Objectives of the G-LESS

The objectives of G-LESS are two-fold: 1) to annually monitor BLLs in children aged 5 to 7 years, nationally and regionally, in order to measure changes over time, and 2) to identify lead exposure sources among children with elevated BLLs.

As primary prevention of lead exposure is the ultimate goal, general exposure source identification is included in the implementation plan for the G-LESS (described in section 10), so that public preventive measures (described section 13) can be put in place, and changes in BLLs can be monitored from year to year with the G-LESS.

5.2 Overview of the G-LESS

5.2.1 Target population

The lead exposure sources in Georgia are not yet known, and there is no information available about correlations in BLLs in mother-child pairs in Georgia. Bone storage of lead in these groups differs greatly: 94% of lead in adult women is stored in bone, compared to 73% in children (15). As release of lead from bone increases during pregnancy due to increased bone remodeling, 10 to 88% of BLLs in pregnant women come from the mobilization of lead from bone stores. Lead content in cord blood has been shown to contain 80% of lead from bone stores. Normally BLLs change rapidly after cessation of exposure (~30 days), but pregnant women's BLLs can continue to be elevated due to the slow release of lead from bone stores. Thus pregnant women's BLLs are influenced to a greater extent by past exposure compared to children's BLLs (15). All this information leads us to the conclusion that monitoring BLLs in children is preferable when the goal is to identify changes in BLLs over time due to changes in lead exposure.

Moreover, as children aged 6 and 7 years have higher BLLs than 2-year-olds (Table 2), it is highly likely that children are exposed to lead after birth as well, possibly from sources other than their mother, in which case source identification in pregnant women will not necessarily prevent high BLLs in children aged 2 to 7 years. Since the goal of the G-LESS is primary prevention (to identify and remove lead sources and measure the effect of the removal), a slightly older age group can be considered and is more relevant for detecting changes over time in response to remediation efforts, as they are no longer breastfeeding, are more exposed to the surrounding environment (run around more) and are easier to sample. Thus, the G-LESS will target children aged 5 to 7 years.

5.2.2 Existing systems and new methods

The Health Management Information System and the Immunization Module

The G-LESS will take advantage of the Health Management Information System (HMIS), which was introduced in 2011 by the Ministry of Health, Labour, and Social Affairs of Georgia (MoHLSA). The HMIS serves as a platform for the electronic registration of health journals, registry data, and surveillance systems. Its components include, among others, the Georgian Birth Registry (GBR), the Vital Registration System (VRS), and the Immunization Module used by the SHP for Immunizations, into which all "immunization centers" (i.e., health care centers as well as rural doctors that provide immunizations to their local community) must register all provided vaccinations (16). Today, Georgia continues to expand the HMIS, for example, with the Covid Registry. All the individual components of the HMIS can be linked using the unique personal identification number that is issued to every citizen at birth.

The G-LESS will be structured to take advantage of the existing, successful SHP for Immunizations. To simplify and optimize the recruitment of children, blood sample collection, BLL testing, results, and follow-up, we suggest adding a Lead Module to the existing Immunization Module and link to information from the GBR and the VRS.

Reasons for adding a Lead Module to the Immunization Module:

- Adherence to child immunizations is high in Georgia (e.g., coverage of the first MMR vaccination [MMR1] was 91.1% in 2020), and most children receive first vaccinations at an early age, at which time they are registered in the Immunization Module.
- The vaccination schedule calls for further vaccinations later in life (at 5 to 7 years of age), at which time children can have a blood sample collected for G-LESS, e.g., at the second MMR vaccination (MMR2).
- The electronic Immunization Module makes it easy to randomly select children and contact their guardians regarding recruitment to G-LESS.
- By law, all immunization centers must record vaccinations in the Immunization Module. Thus, adding the Lead Module to the Immunization Module would ensure complete recording of G-LESS information by providers.

Volumetric absorptive microsampling technique for lead analyses

Traditional lead analyses require whole blood. However, collecting venous blood samples from children is challenging and uncomfortable for the child, and requires centrifugation and freezing. Therefore, instead of venous blood samples, the G-LESS calls for the use of microvolume blood samples, which are collected using a volumetric absorptive microsampling device, or microsampler, that only requires 2 x 20 µL of blood (or 2 drops) which can be obtained by finger prick (Figure 2). Once the drops are collected, the technique fixates the blood sample on an absorptive tip, making it unable to interact with the surrounding environment. If collected properly, the volume of the sample is known accurately, which is important for quantitative purposes. In fact, studies show that when microvolume blood samples were collected in a clinic setting, the sampling success rate was 96% (17). The technique creates samples that are stable for lead detection for at least 3 months at room temperature, so it is very suitable for remote-region sampling. Additionally, the cost of sampling and analyzing microvolume blood samples for lead is not more than that for conventional techniques (Table 8). This is a link to a video describing the sampling technique: https://www.neoteryx.com/how-to-properly-take-a-blood-sample-using-the-mitra-microsampler-vams?hsLang=en

The standard operating procedure for lead analysis in microvolume blood samples was recently validated by the Institut national de santé publique du Québec (INSPQ) and is attached as Supplementary file 1. The standard operating procedure for LIR determination in microvolume blood samples will be provided in September 2022.

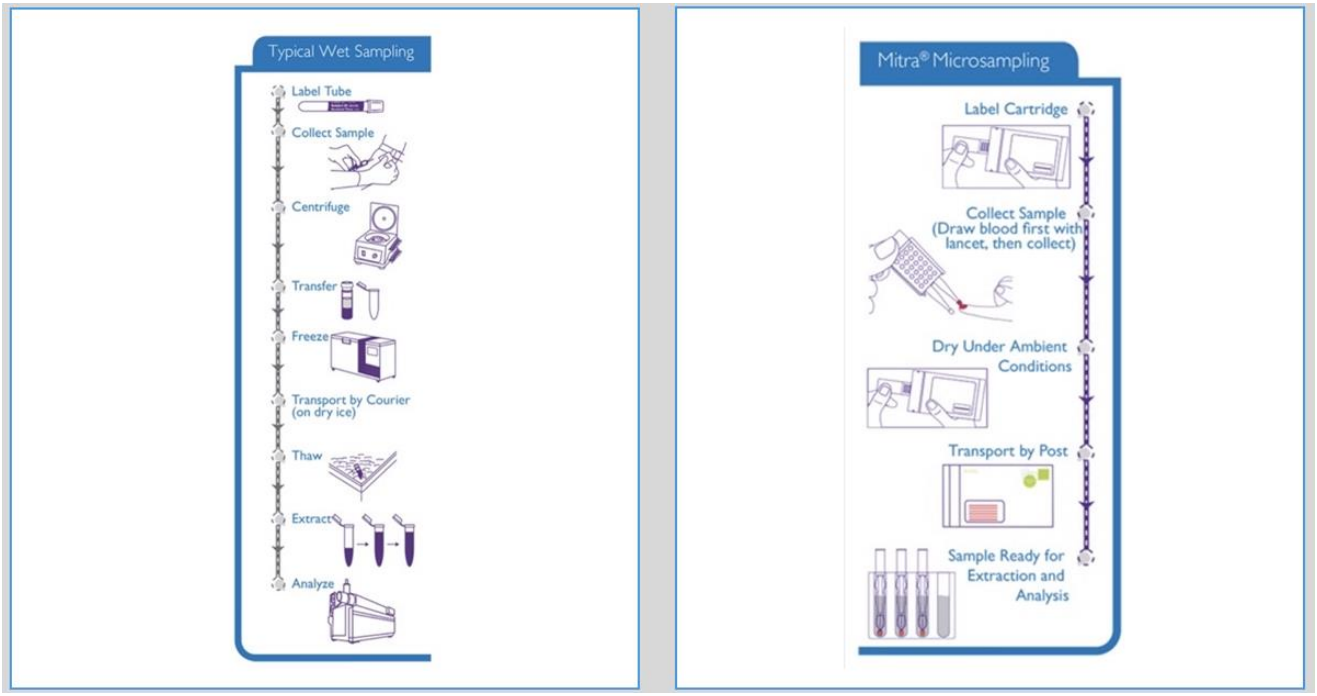

Figure 2. Comparison of sampling, handling, storage, and transportation of conventional blood samples (left) and microvolume blood samples (right).

5.3 Steps prior to recruitment

5.3.1 Creation of a National Expert Group

We recommend that the NCDC's Director General, appoint a National Expert Group (5-6 persons, including international experts), which will have full authority to take necessary actions to implement and manage the G-LESS and will interact directly with the NCDC CRF Research Laboratory and the MoHLSA of Georgia. Dr Gamkrelidze should also appoint the leader of the National Expert Group.

5.3.2 Selection of immunization centers

Immunization centers (i.e., health care centers as well as rural doctors that provide immunizations to their local community) will be responsible for the collection of microvolume blood samples and, in some cases, final recruitment and questionnaires. Using the MMR vaccination as a point of reference, in 2021, around 2500 different immunization centers in Georgia provided MMR vaccination to children aged 1 and 5 years, and 43 immunization centers provided >100 MMR vaccinations (Table 5).

Table 5. Locations of immunization centers that provided >100 MMR vaccinations in 2021 extracted from the Immunization Module. Number of MMR vaccinations is indicated in parenthesis.

Adjara	Batumi (5522)	Khelvachauri (296)	Kobuleti (404)				
Guria	Ozurgeti (194)						
Imereti	Kutaisi (4343)	Sachkhere (345)	Samtredia (487)	Tchiatura (143)	Tkibuli (150)	Zestaponi (816)	
Kakheti	Akhmeta (158)	Dedoflistskaro (130)	Gurjaani (237)	Kvareli (114)	Lagodekhi (114)	Sagarejo (104)	Telavi (582)
Mtskheta-Mtianeti	Dusheti (140)	Mtskheta (121)					
Qvemo Qartli	Bolnisi (105)	Gardabani (349)	Marneuli (954)	Rustavi (2844)			
Samegrelo and Zemo Svaneti	Poti (831)	Senaki (322)	Zugdidi (824)				
Samtskhe-Javakheti	Akhaltsikhe (585)	Borjomi (228)					
Shida Qartli	Gori (1278)	Kareli (121)	Kaspi (195)	Khashuri (602)	Tskhinvali (139)		
Tbilisi	Chughureti (1999)	Didube (3906)	Gldani (4416)	Isani (3476)	Krtsanisi (388)	Mtatsminda(1157)	
Tbilisi	Nadzaladevi (2877)	Saburtalo (6219)	Samgori (3960)	Vake (637)			

However, when these centers are plotted on a map (Figure 3), those providing <100 MMRs per year should also be included in order to cover recruitment in rural regions.

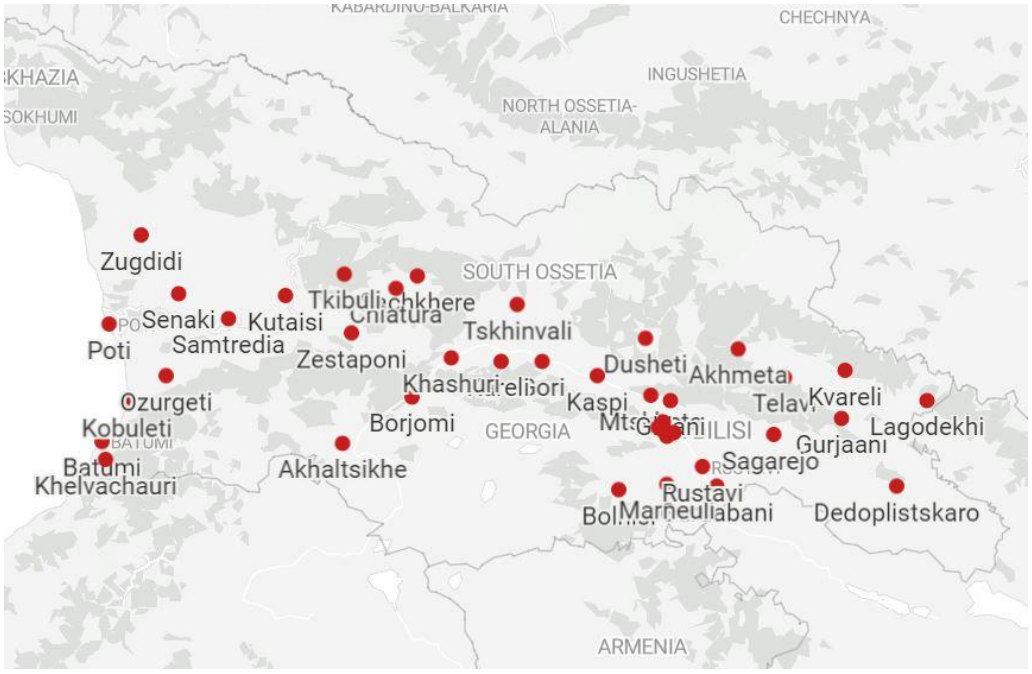

Figure 3. Location of immunization centers providing >100 MMR vaccinations in 2021. Illustration from datawrapper.com.

The National Expert Group needs to determine which immunization centers will participate in the G-LESS from the Immunization Module, according to the following criteria:

1) Location
2) Expected number of immunizations, based on the number of MMR1 vaccinations provided to the targeted birth cohort.

Both public and private centers should be included. Participation should be mandatory, as regulated by a governmental decree. If several immunization centers fulfill the criteria, the National Expert Group should decide which centers to include in cooperation with the NCDC, taking into consideration that some centers may serve certain privileged or unprivileged neighborhoods, and that BLL testing in both is important. Information about maternal education can be extracted from the GBR and checked against certain immunization centers before deciding on which centers to include.

After the immunization centers are selected, a team from the NCDC e.g., the Division of Health Promotion, will hold meetings in each region with representatives from each participating immunization center to offer information and training in the use of the Lead Module and in blood collection procedures. Each center will also receive a pre-determined number of microsamplers at this time, based on the number of children the centers are likely to accommodate. Immunization centers will be reimbursed for each microvolume blood sample collected: we suggest 20 GEL per sample, 10 GEL of which goes to the pediatrician and 10 GEL to the nurse who collected the sample.

5.3.3 Media campaigns

Before recruitment begins, and throughout the life of the G-LESS, the Division of Health Promotion at the NCDC needs to conduct multi-media public awareness campaigns, including TV, posters, social media, and SMS, explaining the rationale for the G-LESS and encouraging individuals to participate.

5.4 Structure and organization of the G-LESS

The structure and organization of the G-LESS is illustrated in Figure 4, and each step is described in more detail below.

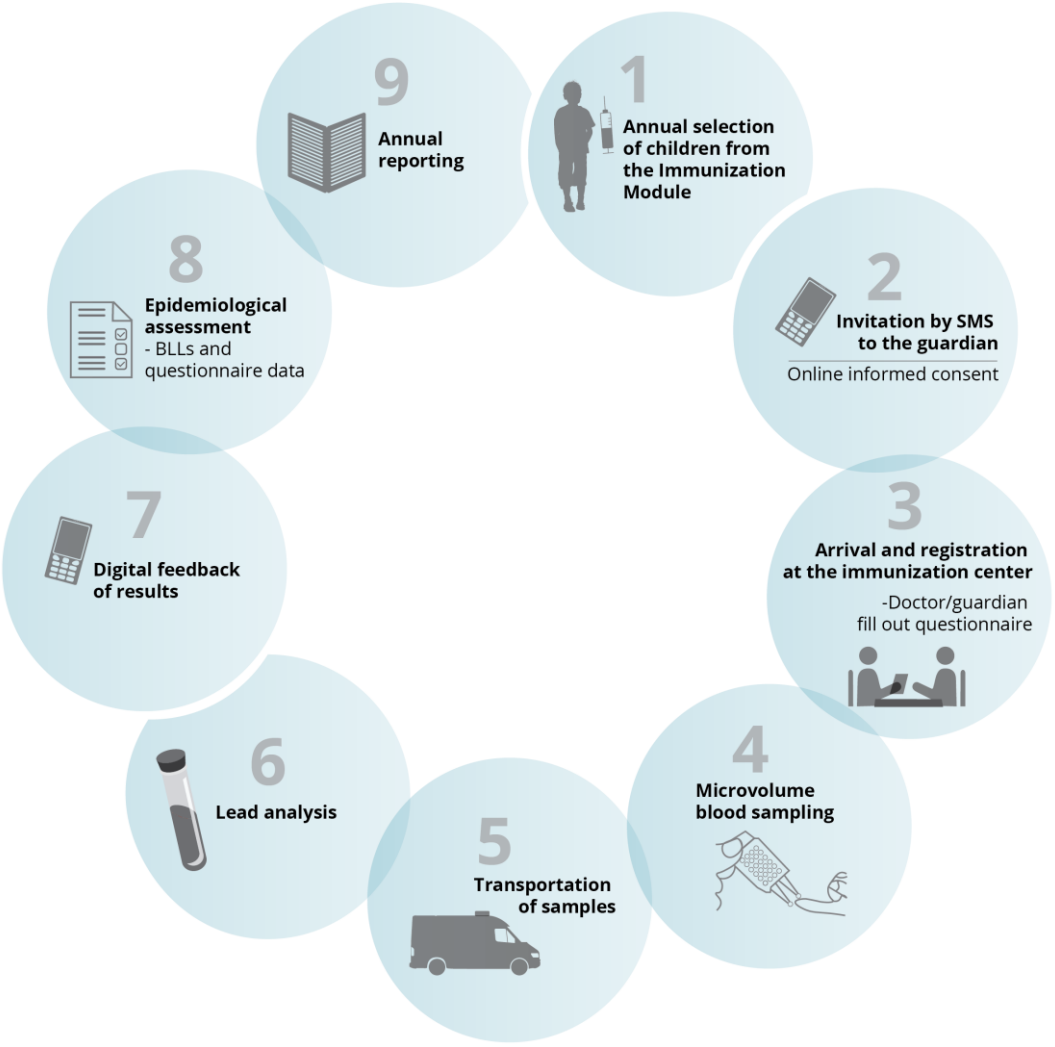

Figure 4. Organization of the G-LESS.

5.4.1 Annual selection of children from the Immunization Module

A random selection of children should be invited to participate in the G-LESS to avoid selection of willing participants, relatives, and neighbors that may have different BLLs than the general population. Note that the random selection of children should be done on a regional level and based on the following criteria:

1) The child is in their 5th to 7th year and scheduled to receive MMR2 or another vaccine within that same calendar year.
2) The child is registered in the Immunization Module.
3) The child received MMR1 at a selected immunization center.

Children who did not follow the Georgian vaccination schedule can still be identified from the GBR, and, if necessary, targeted specifically. The G-LESS will require 4303 participants each year in order to detect a change in BLL of 1 µg/dL per year in each region (Table 6). Note that these calculations are based on random sampling of new children entering their 5th to 7th year annually (independent samples), not repeated measurements of the same children. The last column displays the number of children born in each region in 2020. The sample size calculations are based on data from the 2018 MICS, specifically the standard deviations in each region. To account for non-respondents and the fact that children may move (change address) or change their immunization center, an initial pool of eligible children should be selected at the beginning of each year and should be approximately 3 times larger than the actual target number of 4303, thus around 15,000. After finishing stage 1 and 2 of the implementation process (described in section 10), this pool can be adjusted according to the actual participation rate.

Table 6. Estimated yearly sample size in each region to detect a change in blood lead levels (BLLs) of 1 µg/dL between two independent samples. Equal variances assumed. Estimates are based on data from Multiple Indicators Cluster Survey, 2018.

	Mean (µg/dL)	Standard deviation (µg/dL)	Yearly sample size for detecting 1 ug/dL difference in BLLs	Number of babies born in 2020
Tbilisi	4.5	4.1	292	15657
Adjara	12.1	8.3	1083	5583
Guria	10.4	6.9	749	968
Imereti	7.9	6.9	749	5493
Khakheti	3.8	2.4	92	3520
Mtskheta-Mtuaneti	3.9	3.5	194	843
Samegrelo-Zemo Svaneti	8.2	5.3	442	3054
Samtskhe-Javakheti	5.1	4.3	292	1761
Kvemo Kartli	4.1	3.4	183	5598
Shida Kartli	4.0	3.8	228	2895
Total number of samples per year			**4304**	**45372**

5.4.2 Invitation by SMS to (the child's) guardian

To end up with the correct number of participants per region (Table 6), the children in each region need to be invited in waves. After the initial pool of eligible children has been selected, they need to be divided into two batches for invitation; batch 1 should contain children scheduled to receive MMR2 or another vaccine in the next 6 months; batch 2 should contain children planned to receive MMR2 or another vaccine from months 6 to 12. In month 1, the target number of children in each region should be invited to participate from batch 1. The invitation is sent to the child's legal guardian by SMS. The physical address and telephone number of the mother can be extracted from the GBR and the VRS. In some cases, it may be necessary to link with other components of the HMIS to extract the correct information. The SMS should not be sent out during working hours, or on Friday night. Saturday morning may be a good option.

In the SMS, the guardian is asked if they would be willing to have their child participate in the G-LESS. According to Georgian law, consent from one guardian is sufficient. The SMS will contain a link to the online Lead Module (described in section 6), where the guardian can log in to the guardian-section using their personal id and give informed consent for their child to participate. The consent form should be available in several languages (Georgian, Azerbaijanis, Armenian, and Russian) to cover all ethnic minorities. The SMS should also contain information about which immunization center (the last visited/usual immunization center) the guardian should contact/visit to get the immunization and BLL testing for their child. The SMS should further specify that the invitation to participate in lead testing will expire after 180 days. The SMS invitation should be resent once, after 10 to 14 days, if the guardian has not logged in to the guardian-section of the Lead Module to give consent by that time. For guardians who do not want to, or are unable to complete the consent form online, a paper-based option should be available at the immunization center.

5.4.3 Arrival and registration at the immunization center

Providers at all selected immunization centers must be reminded to register the personal identification number of all children in the Immunization Module upon their arrival (arrival registration), to determine if the child was invited for BLL testing. There are two criteria that need to be fulfilled:

1) The child's guardian has to have received an invitation to the G-LESS, and the child should have arrived at the immunization center specified in the invitation.
2) The invitation must not be older than 180 days.

If these criteria are met, the integrated Lead Module will visually flag the child as invited for BLL testing. Upon arrival registration, the Lead Module will automatically send a new SMS to those guardians who already completed the informed consent form online. This new SMS will contain a link to an online questionnaire, which the guardian must complete. The questionnaire should be short (maximum 15 questions, example in Appendix A) and available in several languages (Georgian, Azerbaijanis, Armenian, and Russian) to cover all ethnic minorities. The provider will also have access to the questionnaire and has the option to interview the guardian/nanny/grandmother and submit the answers. If the guardian has not completed the informed consent form online before arrival registration, and if the child is accompanied by their legal guardian and wishes to participate, the guardian can sign a paper-based informed consent form. In this case the provider should tick a box called "paper-based informed consent" and upload a picture of the signed form to the Lead Module. Another alternative could be to attach the signed paper-based form to the bag that contains the blood sample. It will then be transported along with the sample to the NCDC CRF Research Laboratory and stored in a safe place. Once the provider has ticked the "paper-based informed consent form" box, the online questionnaire will open, and the doctor can interview the guardian and submit the answers. If the legal guardian is not present and has not provided online informed consent, then the child cannot participate in the G-LESS, and the provider should tick the box "Legal guardian not present". There will also be a box for "Decline to participate".

Six months after the first SMS invitation has been sent out, we will have a good estimate of the participation rate and can invite more participants from batch 2 of the initial pool of

eligible children. By selecting 15,000 children, we can reach the annual goal of 4303 participants, even with a participation rate as low as 28%. Note that as the participation rates decrease, the sample may not accurately represent the population. The goal, of course, is to achieve the highest participation rate possible.

5.4.4 Microvolume blood sampling

When the child and the guardian are escorted to the "vaccination room" (the room where the actual vaccine is provided), the provider will enter the child's personal identification number into the Lead Module for dual verification that the child has been invited to participate in the G-LESS, and that all required forms (informed consent, questionnaire) have been completed before moving on to microvolume blood sample collection. Each microsampler will come pre-marked with a sample identification number (sample id), which the provider will enter into the Lead Module. The sample id should be systematic and informative, for instance: "AD2023C1S0001" indicating "Region (Adjara)-year (2023)-clinic#(C1)-sample#(S001)".

Each clamshell box contains two microsamplers. The blood samples are then collected with the microsamplers by finger prick, as per instructions (for a graphic display of the sampling technique, see Appendix B). Each child donates two samples, approximately 1 drop of blood per sample, to ensure enough blood for lead analysis. The microsamplers are kept in the clamshell box, dropped back into their original storage bag, which contains a desiccant, and then stored until shipment. The samples can be safely stored at room temperature for over 3 months. There is no need for freezing or refrigeration.

5.4.5 Transportation of samples

The samples will be shipped to the NCDC CRF Research Laboratory at regular intervals, and at least once a month using the Covid-sample-transport-system. NCDC regional cars will visit each immunization center monthly to pick up the samples and take them to the NCDC CRF Research Laboratory (for handling and shipping instructions, see Appendix C).

5.4.6 Lead analyses

When the samples arrive at the NCDC CFR Research Laboratory, personnel will manually enter the delivery date and the sample ids into the Lead Module, to confirm that the sample was

received. Scanning barcodes, thus entering this information automatically would be preferred, but the current situation in the CRF Research Laboratory does not facilitate this option. Samples should be analyzed no later than 2 months after their arrival. Results will be entered into the Lead Module using the sample id, which is then linked to the child's personal identification number and the guardian's phone number. The guardian will then receive an SMS message informing them that the result is available. They must log in to the guardian-section of the Lead Module and check the result.

5.4.7 Digital feedback - Communication of BLL results and further action

We have been instructed by UNICEF Georgia to adhere to the WHO recommendations for clinical management of exposure to lead as closely as we can (7). The WHO guidelines state "*For an individual with BLL ≥5 µg/dL, the sources of lead exposure should be identified, and appropriate action taken to reduce and terminate exposure*". According to the MICS, 45% of children in Georgia have BLLs ≥5 ug/dL. If the G-LESS covers the recommended 4303 children annually, this would result in exposure source investigations for over 1900 families every year, which we do not find feasible. If we increase this threshold to ≥10 µg/dL, the annual investigations will amount to approximately 800 families. This is still not feasible. Thus, we believe that the way forward is to integrate a systematic exposure source investigation into the national surveillance system in the first years of the G-LESS, as described in section 10 below, and to restrict or remove sources on a national level with the aim of reducing lead exposure for all children in Georgia. Individual lead counselling sessions will be offered to all G-LESS participants with elevated BLLs; in cases with severely elevated BLLs, exposure source investigation and medical intervention may also be required in addition to lead counselling sessions and are described below.

Our recommendations for the communication of BLL results, and interventions in cases of highly elevated BLLs, are outlined in Table 7. These recommendations are based on the WHO guidelines, but we have adapted them according to their feasibility in Georgia. Note that when a child's BLLs is >30.0 µg/dL, the guardian should be contacted by phone immediately, before the results are made available in the Lead Module.

Table 7. Recommendations for the communication of blood lead level (BLL) results to guardians and possible interventions.

BLL	Message to guardian/participant and further actions required	Expected number of children annually[a]
<5.0 µg/dL	Message should read: "Your child's BLL is within normal limits and no adaptations need to be made." General information about possible lead exposure sources and the importance of good nutrition should also be given.	2317
5.0 - 9.9 µg/dL	Message should read: "Your child's BLL is slightly elevated with no immediate cause for concern." Legal guardian should be provided with information about potential lead exposure sources, methods for reducing exposure, and the importance of good nutrition; in particular adequate dietary intake of iron and calcium. The nutritional recommendations should meet the national, age-appropriate recommended nutrient intake values.	1098
10.0 - 29.9 µg/dL	Message should read: "Your child's BLL is elevated and there may be cause for concern". Legal guardian should be provided with information about potential lead exposure sources, methods for reducing exposure, and the importance of good nutrition; in particular adequate dietary intake of iron and calcium. The child should receive several free consultations (including follow-up) by a pediatrician, during which a blood sample for serum ferritin (iron deficiency) should be taken and calcium intake should be evaluated. This could be done by a structured interview based on a targeted questionnaire and evaluated against the national, age-appropriate recommended calcium intake values. Based on the results of serum ferritin, calcium intake and other tests, the child could receive iron and/or calcium supplements free of charge to meet the national guidelines. The child should be offered repeat BLL testing within 12 months.	826
30.0 - 44.9 µg/dL	Before the BLL result is entered in the Lead Module, the guardian must be informed by phone. The conversation should include the language "Your child's BLL is elevated and there is cause for concern." The child should receive several free consultations (including follow-up) by a pediatrician, during which a blood sample for serum ferritin (iron deficiency) should be taken and calcium intake should be evaluated. This could be done by a structured interview based on a targeted questionnaire and evaluated against national dietary guidelines for calcium intake for the specific age-group. Based on the results of serum ferritin, calcium intake, and other tests, the child could receive iron and/or calcium supplements free of charge to meet the national guidelines. The family should be offered a home-visit during which NCDC personally screen the home environment with the XRF instrument. In case of high lead levels, samples from the home environment should be taken as well as an additional blood sample from the child. These samples should be analyzed for lead and highly-contaminated samples for LIRs, in order to exclude or identify possible sources of lead exposure. The child should be offered a repeat BLL testing within 12 months.	56
≥45.0 µg/dL	Before the BLL result is entered in the Lead Module, the guardian must be informed by phone. The conversation should include the language "Your child's BLL is elevated and that there is immediate cause for concern." The legal guardian will be contacted directly, and referred to a specialist that can provide treatment according to best practices. Oral or parenteral chelation therapy is recommended by the WHO. Iron and calcium deficiencies should be evaluated and supplements offered if needed. However, it is imperative that source investigations for these children be prioritized. The family should be offered home-visits, during which NCDC personal will screen the home environment with the XRF instrument. In case of high lead levels, samples from the home environment should be taken in addition to a second blood sample from the child. These samples should be analyzed for total lead, and LIR determination should be performed in samples with high lead content, to exclude or identify possible sources of exposure. The child should be offered repeated BLL testing within 12 months.	6

[a] Estimated number of children from the 4303 participating in the G-LESS. Estimates are based on 2018 MICS results of BLLs in children aged 5 to 7 years.

5.4.8 Epidemiological assessment

After all the data are available electronically (i.e., data on number of invited children, and number of participating children, BLL results, and questionnaire data), additional quality assurance measures should be taken. The data must be assessed by a trained epidemiologist and/or statistician. This person should also have knowledge of the chemical and medical aspects of lead exposure. The dataset must be checked for duplicates, missing values, outliers, and other possible errors. For example, the dataset must be scrutinized to find if the distribution of values for a variable is normal, if it is supposed to be skewed, and if it is skewed in the right direction. This process is crucial for two reasons, 1) to fix problems related to data collection (human error) and 2) to make sure that any numbers or aggregated statistics are correct before reporting. Further, statistics related to response rates, geographical distribution, changes in BLLs from year to year, and associations between BLLs and other collected information needs to be generated.

5.4.9 Annual reporting

Preferably the same person(s) responsible for 4.4.8 should be involved in creating the annual report. Since information from the annual report will likely to be in high demand from several stakeholders, we suggest dividing the annual reporting into two parts. Part 1 will be the proportions and median BLLs only for Georgia and the regions (published in February for the previous year). Part 2 is a more detailed epidemiological report that describes changes, associations, and data inaccuracies that are of particular interest (published in June).

6 The Lead Module

The Lead Module must contain several features:

- The Lead Module must be able to randomly select a certain number of children annually, based on the following criteria: 1) The child is in his/her 5th to 7th year and should receive MMR2 or another vaccine within that same calendar year, 2) The child is registered in the Immunization Module, and 3) The child received the MMR1 vaccine at a selected immunization center.
- The Lead Module must be linked to the GBR and the VRS to 1) identify children who have not received MMR1 and 2) extract the last known address and phone number of the randomly selected participants' guardians. Step 1) is important in order to know how many children are not in the Immunization Module and how they differ from those who received MMR1.
- The Lead Module must be able to automatically send an invitation via SMS to the legal guardian of selected children. As initial oversampling of children is necessary, not all eligible children should be invited at the same time, or there could be more children than there are microsamplers. Children need to be invited in waves, based on participation rates in the different regions. Thus, the manager of the G-LESS needs to be in close contact with the IT Agency under the MoHLSA to update them on the participation rate and determine how many new invitations should be sent every 6 months to reach the target number in each region within a year.
- The Lead Module must be integrated with the Immunization Module, so that selected children are automatically flagged when their personal identification number is entered to register a vaccination. When the invited child's personal identification number is entered, the Lead Module must open a window that allows the provider to enter the sample id written on the microsampler (all microsamplers will be pre-labelled by the manufacturer according to defined sample id criteria). A few quality assurance measures should be added to avoid errors in data entries. The Lead Module should include safeguards to ensure that the sample id: 1) has the correct format, 2) is linked with the correct immunization center, 3) has the correct year, and 4) does not

match any other sample ids already entered. It is very important that the Lead Module has a built-in quality assurance measure that prohibits duplicate records. If the online informed consent form has not been completed before arrival registration, the Lead Module must allow the doctor to tick a box for “paper-based informed consent”, upload a photo of the document, and then access the online questionnaire directly and fill in the questions with the guardian on the spot. The Lead Module must allow the doctor to tick a box for “legal guardian not present” in case the child arrives at the immunization center with a nanny, and the guardian has not completed the online informed consent form. It must also allow the doctor to tick a box for “decline to participate”.

- The Lead Module must register that a collected microvolume blood sample is ready for pick up and transport using the existing Covid-sample-transport-system.
- The personnel at the NCDC CRF Research Laboratory must be able to log into the Lead Module and enter the sample id, the date the sample was received, and BLL results. The sample id should then be used to link the BLL results to the child’s personal identification number. Thus, it is important that NCDC personnel not be able to submit BLL results if 1) the sample id has the wrong format, 2) the sample id does not match the sample id entered at sample collection, and 3) the BLL is outside of maximum pre-defined levels. The Lead Module must also be able to use the guardian’s stored phone number to send an SMS informing the guardian that BLL results are available and can be accessed by logging in to the guardian-section of the online Lead Module. The SMS should also include a phone number that guardians can call to receive the BLL results in case they cannot access the online Lead Module from their phone.
- The Lead Module must contain an option to add LIR results from blood and environmental samples collected during individual exposure source investigations among children with high BLLs.
- The Lead Module must also have an online component with a guardian-section, where guardians can log in to provide online informed consent, answer the questionnaire, and receive BLL results.

7 Involved agencies

We recommend that the NCDC's Director General, appoint a National Expert Group (5-6 persons, including international experts), which will have full authority to take necessary actions to implement and manage the G-LESS. Several divisions at the NCDC need to be involved, including the Division of Environmental Health, the Division of Health Promotion, the Division of Immunization, and the CRF Research Laboratory. The MoHLSA needs to be involved in the development of the necessary governmental decrees listed under section 10, stage 0. We are aware that at present, the Ministry of Environmental Protection and Agriculture is responsible for evaluating lead in food and environmental risk factors according to the State protocol for early detection and management of lead poisoning in children (13). However, it is important that responsibilities related to G-LESS lead exposure source investigations be conducted by the NCDC, to avoid fragmentation of responsibilities, and ensure that sampling and analysis are performed in the same way, by the same personnel, and on the same instruments for all samples. The IT Agency under the MoHLSA must be involved in the development of and improvements to the Lead Module, as well as in data extraction.

8 Data management and reporting system

All data should be entered and stored in a single database, including, but not limited to, informed consent forms, questionnaires, BLLs, and LIRs determinations of children with elevated BLLs. This is preferable to combining different sources (and possibly file formats) later. The easiest way to achieve this is to enter everything directly into the Lead Module, in the same way that maternal and child information is currently entered directly into the GBR. The information in the Lead Module needs to be stored in a safe, cloud-based location like the other components of the HMIS. Personnel should be able to extract and export raw data from the Lead Module to different statistical software.

Although it is technically achievable to develop a system that automatically generates results from entered data, we strongly advise against this practice. All data should be checked by a qualified epidemiologist/statistician for added quality assessment.

9 Continuous evaluation and adaptation of the G-LESS

Based on our previous experiences implementing surveillance systems, we can say with confidence that continuous evaluations and improvements will be needed throughout the lifetime of the G-LESS. It is impossible to predict all the challenges that will present themselves during the implementation of a new nationwide system. To exemplify, quality assurance measures may need to be developed and improved in order to avoid erroneous data. For example, if we allow open entries of BLLs (from 0.0 - 1000) without scrutiny, 10.0 can easily become 100 (a wrong entry), resulting in outliers and skewed data. Other challenges can sometimes be much harder to detect, such as systematic errors coming from a single immunization center, or other discrepancies that can only be identified through detailed data scrutiny. Therefore, we also suggest a step-wise introduction of the surveillance system, as described in section 10.

10 Implementation

We believe that ownership of the G-LESS and proper political will to support its development are the most important factors for the successful implementation of this surveillance system.

10.1 Stage 0: Planning and development

1. Georgian authorities must decide whether they want to implement the G-LESS. If yes:
2. A National Expert Group (5-6 persons), including international experts, should be appointed by the NCDC and will have full authority to implement and manage the G-LESS, interacting directly with the NCDC and the MoHLSA from stage 0 and until full-scale implementation.
3. A governmental decree is needed to:
    a. Allocate a budget for implementing and running the G-LESS.
    b. Order the IT Agency under the MoHLSA to develop the electronic Lead Module described in section 6.

c. Describe responsibilities and legal requirements. We strongly recommend that the NCDC be the institution responsible for all analyses, including blood, food, air, water, paint, soil, etc. for the specific purpose of identifying lead exposure sources.
d. Order certain immunization centers (also rural doctors) to participate in the collection of microvolume blood samples for the G-LESS.
e. Outline the criteria for reimbursement to immunization centers/doctors/nurses.
f. Describe whether the G-LESS should have its own budget or gradually replace the SHP for Lead Biomonitoring.

4. Together with the National Expert Group, an expert in the development of health IT solutions, for example Alexander Turdziladze, must develop a Technical Specification Document that describes the details of the Lead Module that should be developed. The document should contain information about how the Lead Module will behave, what it can and cannot do, how it will be developed, development of security and data privacy measures, a plan to test the system, support and maintenance plans, and a system creation timeline. Several of the components needed for a Technical Specification Document have been described in section 6, but they need to be further developed by an IT expert.
5. Based on the Technical Specification Document, the IT Agency under the MoHLSA must develop the Lead Module, which will be permanently connected to the Immunization Module, the GBR, and the VRS. This includes algorithms for the random selection of children based on selected immunization centers. This step may take time.

10.2 Stage 1: Initial implementation, evaluation and source identification

Objectives:

i. Implement and evaluate electronic recruitment to and participation in the G-LESS.
ii. Identify primary sources of lead exposure.

It is highly likely that more important information concerning lead exposure sources will become available before stage 1 is initiated. As results come in, adjustments will have to be made to the design of source identification in stage 1. The design will also depend on available budget, capacity at the NCDC CRF Research Laboratory, and priorities regarding which hypothesis to focus on, for instance the west-east gradient, dietary exposure or atmospheric deposition. Thus, an important job for the National Expert Group will be to thoroughly evaluate all available scientific evidence of lead exposure sources, and design the best possible source investigation within the allocated budget. Below is an initial suggestion:

1. Select immunization centers in Adjara and e.g. Imereti. Note that they should be geographically spread within each region.
2. Translate the pamphlet describing the procedure for microvolume blood sample collection to Georgian.
3. Train doctors and nurses at the selected immunization centers, including handling of the Lead Module, microvolume blood sample collection, handling of microsamplers, and sample transportation.
4. Distribute microsamplers, sampling instructions, and video to the selected immunization centers.
5. Generate a random selection of children based on the selected immunization centers and age. Divide the selected children into two batches according to the timing of scheduled vaccinations (more details in section 5.4.1 and 5.4.2). Send invitation SMS to legal guardians.
6. Month 1: Send 250 invitation SMSs to legal guardians in Adjara and to 250 in Imereti.

7. Month 6: Evaluate the response rate in each region. Response rate is here defined as how many of the invited children attend BLL testing at the correct immunization center within 6 months. For example, if the participation rate is 50%, then 250 new children must be invited from Adjara and 250 from Imereti.
8. Repeat step 7 until 250 children in Adjara and 250 in Imereti are enrolled.
9. Continuously transport samples to the NCDC CRF Research Laboratory to be analyzed consecutively.
10. After all samples are analyzed for BLLs, select several children in Adjara and Imereti for further investigations of LIRs in blood and household samples. We suggest consulting the INSPQ in Canada to determine the number of children to be selected in each region and follow their recommendations for the best approach according to the current state of available evidence for lead exposure sources identification. Children with BLLs ≥30µg/dL should be followed up according to Table 7.
11. The NCDC should contact guardians and perform home-visits of selected children. During the home-visit, a new microvolume blood sample should be taken from the same child (or a venous blood sample, if the LIR determination is not yet in place for the microvolume blood samples, or not sensitive enough). Use XRF to systematically measure lead in solid materials. Every measurement needs to be registered in the Lead Module, including measurements that are below the XRFs limit of detection. It is important that the same solid materials are measured in every household. The National Expert Group should also consider collecting information about the quantity of exposure from every child through interviews or questionnaires. Based on the XRF measurements and quantity of exposure, collect ~10-15 samples from each household for LIR measurements. A governmental order will be needed to allow the NCDC to sample food.
12. In stage 1, we suggest that samples be sent to the INSPQ in Canada for LIR determinations. This step is to secure a fast and accurate determination, as it may take time before the NCDC CRF Research Laboratory is ready to perform LIR analyses themselves. Simultaneously, the CRF Research Laboratory can measure LIRs in some selected samples to compare results with the INSPQ.

13. As described in section 6, all data on BLLs and questionnaires from the 250 children from Adjara, the 250 children from Imereti, XRF measurements from all households, lead and LIR results from blood and household samples must be registered and stored in the Lead Module.
14. Statistical analysis of all collected data. Steps to consider:
    i. How to handle measurements with concentrations lower than the method's limit of detection.
    ii. Evaluate BLLs in relation to geographical locations (within and between regions).
    iii. Compare differences in BLLs according to age, diet, and other data from the questionnaire.
    iv. Interpretation of LIRs in blood and household samples in individual children and collectively.
15. Evaluate the recruitment procedure, response rate, blood sample collection, transportation, and the electronic Lead Module:
    i. Evaluate workflow and responsibilities. Benefits and challenges related to the continuous recruitment of children.
    ii. Response rate and recruitment process: Did SMS recruitment and online consent form work as expected? Did the response rate vary according to geographical location between and within regions? Did it vary with maternal education (extracted from the GBR) and whether the child had followed the national immunization schedule?
    iii. Length of questionnaire should be evaluated. Were the questions informative? After additional information from the LIR measurements, should some questions be replaced? Can the questionnaire be used to identify children with high BLLs?
    iv. Perform interviews with selected doctors/nurses about possible challenges revealed during recruitment/sampling/transportation, and how they can be improved.

v. How large was the proportion of samples lost during transport? Calculate number of days between sampling and analysis. Did this effect the BLLs?
vi. How many of the received samples had too little blood, or too much blood?
vii. Evaluate home-visits, analysis, and reporting with the available work force in the CRF Research Laboratory. How many samples can be analyzed per day? What needs to be improved to scale up the G-LESS?

16. Implement improvements of all components of the G-LESS according to evaluations and lessons learned.
17. If sources of lead exposure are identified, a governmental order to restrict use/exposure must be made, and a public awareness campaign about how to reduce lead exposure should be performed.

10.3 Stage 2: Scaling up the G-LESS

If sources of lead exposure are not identified in stage 1 or from other initiatives/independent investigations, more LIR determinations need to be conducted in stage 2.

Objectives:

i. To implement the improvements in the G-LESS identified in stage 1.
ii. To include immunization centers from more regions in the G-LESS.
iii. Further evaluations of the G-LESS.
iv. Potentially further source investigations.

1. Full-scale implementation of the G-LESS in Adjara, Tbilisi, and Imereti (n=2124). Sample size according to Table 6. This step includes recruiting new immunization centers.
2. Training of doctors/nurses in selected immunization centers.
3. Recruitment of children in waves in each region as described in sections 5.4.1 and 5.4.2. The number of children invited in month 1 should be adjusted according to the response rate identified in stage 1.
4. All generated data should be registered and stored in the Lead Module.

5. Statistical analysis of changes in BLLs in Adjara and Imereti from stage 1 to stage 2, as well as associations between questionnaire data and BLLs.
6. Evaluations according to step 15 of stage 1
7. Improvements of the electronic system, logistics, and sample handling according to evaluations.

10.4 Stage 3: Full-scale implementation of the G-LESS

If sources are not identified in stage 1, stage 2, or from other initiatives/independent investigations, more LIR determinations need to be conducted in stage 3.

Objectives:

i. To implement improvements to G-LESS from stage 2.
ii. To include immunization centers from all regions in the G-LESS.
iii. Further evaluations of G-LESS.
iv. Potentially further source investigations.

1. Full-scale implementation of G-LESS in all regions in Georgia. Sample size according to Table 6, i.e., 4303 children in total. This includes recruiting all immunization centers.
2. Training of doctors and nurses.
3. Recruitment of children in waves in each region as described in sections 5.4.1 and 5.4.2, adjusted according to the response rate identified in stage 1.
4. All data should be collected in the Lead Module, as in stage 1.
5. Statistical analysis of changes in BLLs in Adjara and Imereti from stage 1 to stage 2 and to stage 3, as well as associations between collected questionnaire data and BLLs.
6. Evaluations according to step 15 of stage 1.
7. Improvements to the electronic system, logistics, and sample handling according to evaluations.

11 Competence needed to implement and manage the G-LESS

- Manager from the NCDC (100% position) and part of the National Expert Group. After full-scale implementation, the manager will be main responsible for all steps in G-LESS. Preferably a person with competence in epidemiology and statistics.
- Personnel responsible for training doctors and nurses i.e., the NDCD Division of Health Promotion.
- Epidemiologist/statistician involved in designing the Lead Module, including a cloud-based database for storing all lead-related data. In stage 0-3 this function may be covered by the National Expert Group; however, the competence for this function needs to be developed locally.
- Epidemiologist/statistician responsible for data analysis. This person should preferably have some knowledge or acquire knowledge about chemical analysis and pollutants. This person should work in close collaboration with the NCDC CRF Research Laboratory and other experts. In stage 0-3, this function may be covered by the National Expert Group; however, the competence for this function needs to be developed locally.
- Personnel responsible for contacting guardians of children with high BLLs and for answering questions from immunization centers and families regarding medical management and technical errors with the Lead Module.
- 3-4 full time chemists in the NCDC CRF Research Laboratory to handle all planned samples.
- 2 people (part-time) performing home-visits and sampling of highly exposed individuals. The same people should perform all home-visits, so that all measurements and sampling are conducted in the same way and with the same methodology and instruments.

12 Estimated costs

Table 8 estimates the one-time and running costs of the fully implemented G-LESS. Transportation of samples from the immunization centers to the NCDC CRF Research Laboratory is not included, nor are salaries for NCDC staff. Estimated costs are based on information from the producer of the sampling devices for microvolume blood samples (Neoteryx) and from cost estimations from the INSPQ and NILU laboratories.

Table 8: Estimated one-time and running costs of the G-LESS

	Amount	Price per unit (EUR)	Total (EUR)
The Lead Module			
Development of Technical Specification Document			5,000-7,000
Development of the Lead Module (year1)			30,000-35,000
Further development of and improvements of the Lead Module			5,000-10,000
Total cost related to the Lead Module			**40,000-52,000**
Annual costs for the full surveillance system			
Microsampling devices and analysis of lead in microvolume blood samples[a]	4303	15	64,545
Reimbursement to pediatricians and nurses	4303	6	25,818
Follow-up of highly exposed children [b]			
Individual lead counselling sessions and medical follow-up [c]	888	36	31,968
Retesting of BLL within 12 months [d]	888	15	13,320
Lead analysis in environmental samples [e]	620	15	9,300
LIR determinations in samples from highly exposed individuals and their home environment [f]	682	10	6,820
Total annual costs (EUR)			**151,771**

[a] Estimated costs per sampling device is 5-10 EUR; lead analysis is estimated to 5 EUR per sample including all consumables and chemicals needed. Argon gas for the ICP-MS instrument is not included in the estimations.
[b] These costs will be reduced over time with cessation of lead exposure.
[c] Costs are based on numbers from the SHP.
[d] Costs include sampling devices and lead analysis as described in [a] .
[e] Costs includes sampling devices (2-5 EUR) and lead analysis (10 EUR).
[f] Estimated costs for LIR measurements in microvolume blood samples and in environmental samples (10 EUR per sample). Costs for sampling devices are included in [a, d] and [e].

13 Public health preventive actions

Lead surveillance of Georgian children must be a long-term commitment, as identification, removal of lead exposure sources, and possible remediation is a process that takes many years. Since Georgia seems to be ready to replace its secondary preventive measures (the SHP) with a primary prevention approach (G-LESS), the next natural step is to restrict public access to primary lead exposure sources, when they are identified.

Specific public health preventive actions to consider:

1) Changes in legislation that will facilitate prohibition of sale of certain types of consumer goods with high lead levels.
2) More comprehensive, regular and better targeted monitoring of consumer products that may contain lead. Both the monitoring strategies and results of the monitoring should be made publicly available.
3) The introduction of preventive legislation and more effective enforcement of available legislation, to allow for punitive actions against polluters.
4) Finance known and effective remediation of lead-contaminated areas.
5) Financing schemes for individuals to improve lead-contaminated home environments, for example removal and replacement of old leaded paint in private houses.
6) A nationwide dietary assessment of macro- and micronutrient intake among children in Georgia should be considered.
7) Public campaigns to raise awareness about how to prevent lead exposure.
8) Continuous monitoring of BLLs through the G-LESS for at least the next 15 to 20 years.

14 Data sharing

During the drafting of the present report, it became apparent that there is a lot of data available from lead investigations that have not been shared or collectively evaluated across and within agencies. For instance, BLLs in children and family members generated by the SHP for Lead Biomonitoring, and XRF measurements in selected households from beneficiaries of that facet of the SHP, are not merged and collectively evaluated. We believe that this could be important information when trying to identify possible lead exposure sources. Data from the continuous monitoring of lead in products like petrol and food, and the specific results from individual samples, including information on origin and sampling methodology, should be made available. Additionally, there are different research environments that perform different investigations, but do not seem to coordinate with each other.

15 Recommendations for the CRF Research Laboratory

These recommendations are based on a ½ day visit to the NCDC CRF Research Laboratory. A more detailed description can be made if the team from Norwegian Institute for Air Research is hired for laboratory training. Several consumables are needed per microvolume blood sample and per environmental sample, which are necessary to maintain workflow and can be estimated from the standard operating procedures.

Based on the project group's collective experience from many decades of laboratory analysis of heavy metals, it takes time to set up new laboratory methods and train personnel in sample preparation, analysis, instrument maintenance, troubleshooting, interpretation of data, etc. Full capacity cannot be expected until after 12-18 months of continuous training, evaluations, and improvements.

Recommendations for the CRF Research Laboratory:

- The lab should focus on implementing methods for lead analysis. Methods for other types of contaminants (organic pollutants) can be implemented at a later stage.
- The number of samples analyzed in the NCDC CRF Research Laboratory should be gradually increased.
- To analyze around 4300 blood samples and 600 environmental samples per year, a minimum of 3 full-time chemists are needed.
- A digestion block for digestion of microvolume blood samples should be purchased to increase capacity and facilitate the preparation of blood samples. The standard operating procedure for sample preparation of microvolume blood samples is attached as Supplementary File 1. The standard operating procedure for analysis of lead in conventional blood samples is attached as Supplementary file 2.
- The microwave oven should be used for digestion of environmental and food samples, not for microvolume blood samples. The standard operating procedure for sampling and analysis of food samples is attached as Supplementary file 3.
- The CRF Research Laboratory should purchase Standard Reference Material (SRM 1566b-Oyster Tissue) from National Institute of Standards and Technology (NIST) to monitor the accuracy of the lead measurements. One SRM sample should be prepared and decomposed in every digestion cycle.
- To work efficiently, one person should be responsible for sample preparation, and one person for analysis on the Inductive Coupled Plasma Mass Spectrometry Mass Spectrometry (ICP-MS-MS) instrument.
- It is recommended that laboratory staff have access to computers that are not connected to the analytical instruments. This will enhance the efficiency of laboratory workflow by allowing staff to do necessary quality control and calculations without stopping the instrument from running.
- Environmental and blood samples have complicated matrices that will contaminate the interior of the mass spectrometer over time. To minimize this contamination,

we recommend that the laboratory acquire a sampling introduction system for discrete samples (ISIS, Agilent).

- Analysis of 4303 blood samples and 600 environmental samples a year will generate a large amount of data. Connection to a server for traceability and safe storage of raw data, quality assurance-quality control data, calculations, and reports are strongly recommended.
- Use of an internal standard should be implemented in all ICP-MS-MS methods.
- There is a lack of general “glassware” in the laboratory, and supplies are needed.

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17 Appendix A: Example of questionnaire

The legal guardian will either complete the questionnaire online, or they will be interviewed at the immunization center and the doctor will add the information to the Lead Module. It is important that the questionnaire be user friendly and not too time consuming to complete (maximum 10 minutes). Note that the questionnaire needs to be carefully developed according to the available level of evidence of lead exposure at the current time. The questionnaire should also be evaluated during the implementation phase and adjusted accordingly.

Below are examples of questions that may be relevant to include in the questionnaire.

General information

1. Who responded to the questionnaire (if filled out by the doctor)? Legal guardian/grandmother/nanny?
2. What is the child's region of residence?
3. Write the name of the town/settlement/village where the child lives.
4. How long has the child lived in the current town/village?
5. If the child has moved, where did the child live before?
6. What kind of property does the child live in? Flat/house/cottage.
7. What is the standard of the housing? New building/old building (more than 30 years old)/ newly refurbished building.
8. Are there painted interior walls in the house/flat where the child lives? Yes/no.
9. If yes, when was this done and what kind of paint was used?
10. Are there painted exterior walls in the house where the child lives? Yes/no.
11. If yes, when was this done and what kind of paint was used?
12. What kind of car do you have in the household? Diesel car/gasoline car/both/no car.
13. If you have a car in the household, from where do you buy your diesel/gasoline?

Information about the child

1. What is the current height of the child?
2. What is the current weight of the child?

Diet

Note that these are just examples, and that the final questionnaire needs to be carefully developed.

1. How often do you use the following spices in your cooking? Note that the types of spices may have to be modified based on the best available data at the time.

   Svaruri Marili? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

   Kviteli kvavili? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

   Khmeli suneli sharcho? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

   Turmeric? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

   Utsko suneli? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

2. From where do you buy your spices?

   Svaruri Marili? Grocery store/bazars/home grown/home-imported

   Kviteli kvavili? Grocery store/bazars/home grown/home-imported

   Khmeli suneli sharcho? Grocery store/bazars/home grown/home-imported

   Turmeric? Grocery store/bazars/home grown/home-imported

   Utsko suneli? Grocery store/bazars/home grown/home-imported

3. How often does your child eat cheese? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day
4. How often does your child drink milk? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day
5. How often does your child eat food cooked in milk? Never_seldom/1 time per week/2-4 times per week/ 5-6 times per week/ 1 time/day/ More than 1 time per day

Toys

1. What kind of toys does your child have? Toys bought from the store/ Homemade toys? Etc.
2. If you child has any homemade toys, which material are they made of? Wood, painted wood, metal, painted metal, wool/yarn

Comments

Open box for feedback/comments should be available at the end of the questionnaire

18 Appendix B: Sample collection in the field

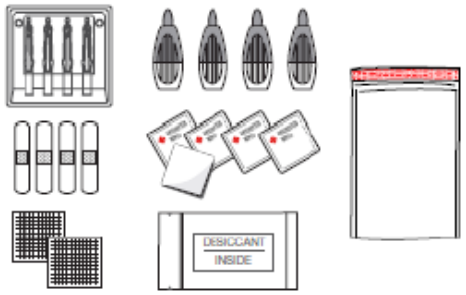
Collection Convenience Kit Containing a Mitra® Clamshell
Follow these steps to correctly collect and transport blood microsamples.

Step 1
Remove components from kit and lay them out.

Mitra 4-sampler Clamshell (x1)
lancet (x4)
adhesive bandage (x4)
alcohol prep pad (x4)
gauze sponge pack (x2)
aluminum bag with desiccant (x1)
prepaid padded shipping envelope (x1)

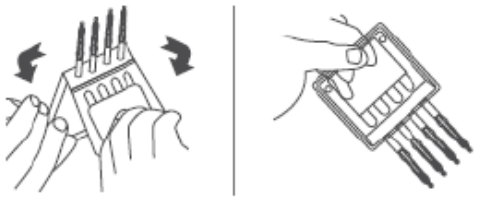
Items needed, not included in kit:

Warm, soapy water (step 3)
Warm, moist towel (step 5)



Step 2
Open clamshell by pulling apart the sides and pressing them together to form a handle.

IMPORTANT!
- **Do NOT remove microsamplers from clamshell**



Step 3
Identify the desired puncture site (shaded area).

Wash your hands thoroughly with warm, soapy water. Rinse and dry.

Step 4
Use a warm, moist towel for three minutes to warm puncture site.

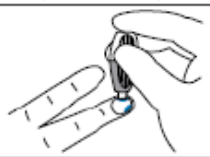
Then clean fingertip with alcohol prep pad provided and allow to completely dry.

Step 5
Twist off tab to break the seal and discard.

reference: BD Microtainer® Contact-Activated Lancet Quick Reference Card (https://www.bd.com/vacutainer/pdfs/VS7536.pdf). See included insert.

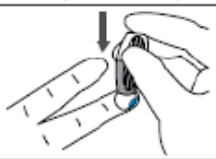
Step 6
Position safety lancet firmly against puncture site as illustrated.
Hold safety lancet between fingers.

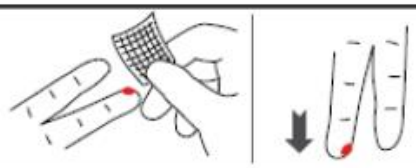
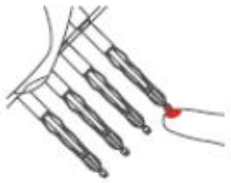
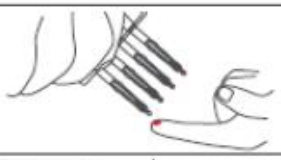
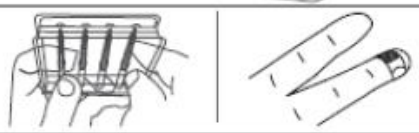
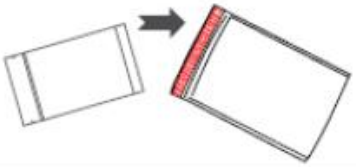
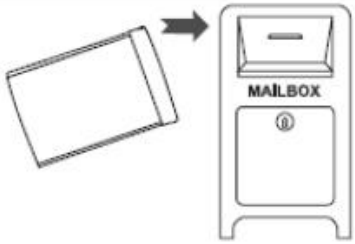
reference: BD Microtainer® Contact-Activated Lancet Quick Reference Card (https://www.bd.com/vacutainer/pdfs/VS7536.pdf). See included insert.



Step 7
To activate, press safety lancet firmly against the puncture site.
Do not remove the device from the site until an audible click is heard.
Discard used safety lancet into an approved sharps container.

reference: BD Microtainer® Contact-Activated Lancet Quick Reference Card (https://www.bd.com/vacutainer/pdfs/VS7536.pdf). See included insert.



Step 8 Wipe off first blood drop with gauze sponge provided. Position hand downward towards floor allowing gravity to help increase blood supply to the punctured finger and allow second blood drop to form.	
Step 9 One at a time, apply microsampler tip to the surface of the blood drop. Watch sampler tip turn FULLY red and then count 2 additional seconds. SLOWLY and SMOOTHLY remove microsampler tip from blood. **IMPORTANT!** • **Tip should always point downward towards floor** • **Do NOT drop blood onto the tip from above**	
Step 10 Repeat step 8 with remaining microsamplers in Clamshell. If more blood is required to fill the remaining microsamplers go back to step 3 and use a new lancet provided in the kit.	
Step 11 Unfold Clamshell to cover microsamplers and press firmly on both sides until a click is heard and place on surface. Apply adhesive bandage to lancet puncture site.	
Step 12 Microsamplers secured in Clamshell should be immediately placed in provided aluminum bag containing desiccant and SEALED tightly using the zipper-top closure.	
Step 13 Place the SEALED aluminum bag in the provided prepaid padded shipping envelope and seal it using the adhesive strip.	
Step 14 Insert your SEALED prepaid padded shipping envelope into a mailbox.	

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19 Appendix C: Shipping Guidelines for Dried-Blood Spot Specimens

Shipping Guidelines for Dried-Blood Spot Specimens

Dried-blood spot specimen collection	Healthcare professionals collect dried-blood spot (DBS) specimens by carefully applying a few drops of freshly drawn blood from a finger stick or a heel stick onto specially manufactured absorbent specimen collection (filter) paper. The blood saturates the paper and should be air-dried for a minimum of 3 hours. The Clinical and Laboratory Standards Institute has published specimen collection techniques and specifications for FDA-approved absorbent filter paper as national standards.[1]
Uses for dried-blood spot specimens	After collection, DBS specimens are shipped to public health laboratories by mail, courier service, or express delivery service. Technicians then subject the specimens to various analytical procedures. One of the most important DBS uses is screening the more than 4.2 million infants born annually in the United States for congenital and inherited metabolic disorders. Other important applications include DNA/RNA molecular methods; forensic studies; immunologic studies; and nutritional evaluations of infants, children, and adults.[2]
Regulations for shipping dried-blood spot specimens	The U.S. Department of Transportation (DOT)[3-4] and the United States Postal Service consider DBS specimens nonregulated, exempt materials. DOT has harmonized its regulations[5] with the regulations issued by the ▪ International Air Transporter Association (IATA),[6] ▪ World Health Organization's Guidance on Regulations for the Transport of Infectious Substances,[7] and ▪ International Civil Aviation Organization's Technical Instructions for Safe Transport of Dangerous Goods by Air.[8]
Considerations when shipping dried-blood spot specimens	DBS specimens can be shipped by mail or other carrier with no reasonable expectations of occupational exposure to blood or other potentially infectious material. Use "standard precautions"[9] when collecting and preparing DBS specimens for shipment. Comply with local regulations and institutional policies.

Proper packing essential	Even though DBS are classified as nonregulated, exempt, you must properly package and label the specimens for shipping. Proper packaging and labeling notifies employees and transportation personnel of your package's contents and meets the Domestic Mail Manual (DMM) 601.10.17.8 guidelines.[10]
Triple-packaging dried blood spots for shipment	To mail DBS specimens, you must use the basic triple-packaging system. 1. The primary container is the filter paper matrix that contains the absorbed and dried blood. 2. A secondary container must enclose the primary (filter paper) container. The secondary container should have a fold-over flap or an inner envelope to secure the contents. 3. The third level of containment is an outer envelope of sturdy, high-quality paper. These levels of containment provide reasonable safety from occupational exposure and maintain optimal specimen integrity.[7]
Preparing the outer shipping container	▪ The outer shipping container must have a complete return address and delivery address. ▪ No content markings are required on the outer shipping container.[10] ▪ You must affix or print the international biohazard symbol on the either the primary or secondary container to meet U.S. Occupational Safety and Health Administration requirements.[11]
Additional shipping considerations	We do not recommend shipping packaged DBS specimens in plastic, foil bags, or other airtight, leak-proof sealed containers. The lack of air exchange in the inner environment of a sealed container causes heat buildup and moisture accumulation.[1] Heat, direct sunlight, humidity, and moisture are also detrimental to the stability of DBS specimens and to analyte recovery. The inclusion of desiccant packs with the primary container will aid in preventing moisture accumulation. But remember that shipping conditions are uncontrolled, and desiccant has limited effectiveness.

Local regulations might require plastic or foil shipping bags	Always follow local postal, courier, and other transport regulations. If local regulations require enclosure in airtight, leak-proof sealed containers (plastic or foil bags) for transportation, then you must include a sufficient number of desiccant packages to ensure specimens are exposed only minimally to excessive moisture. You can also use indicator cards monitor humidity.[1]
Shipping specimens that contain an infectious agent	When shipping specimens known to contain an infectious agent, use special precautions and follow international, national, and local regulations (e.g., required packaging and an outside warning label).

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