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ABSTRACT PREVIEW: RE-EXAMINING THE TREATMENT OF LEAD-EXPOSED CHILDREN TRIAL: IMPACT ON GUIDELINES AND POLICY

Re-Examining the Treatment of Lead-Exposed Children Trial: Impact on guidelines and policy

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Author(s)

DS

Daniel P. Schwartz, MS2

Position:
2nd Year Medical Student

Organization:
University of Arizona College of Medicine-Phoenix

Role:
Author

Biographical Sketch

Daniel (“Danny”) Schwartz is a second-year medical student at the University of Arizona College of Medicine–Phoenix and co-founder of the Environmental and Occupational Medicine Interest Group, which focuses on environmental and occupational health in Arizona communities and connects students with opportunities to explore this field as a career.

His research interests include biomonitoring, public health policy, and metal/metalloid exposure. Originally from Oregon, Daniel became interested in medicine near the end of college after an episode of black mold exposure. He graduated with a B.A. in Romance Languages and then took several gap years, during which he worked and completed the science coursework needed for medical school. He worked as a construction laborer and later in an inorganic chemistry lab designing novel metal–ligand complexes, experiences that sparked his interest in toxic metal exposure pathways. Although his initial interest centered on exposure to lead-based paint, this is relatively uncommon in Phoenix, where he now lives, and his interests have since expanded to arsenic and uranium exposure from drinking water and mining activities in Arizona.

He currently serves on the advisory panel of the Four Corners States Biomonitoring Consortium, an AZDHS/CDC program which monitors metals and metalloids in urine samples among people living near mines.

ACOEM Member
Yes

Disclosure Status: Complete
Disclosure: Nothing to Disclose
Signed: *Daniel Schwartz* (11/12/2025, 2:00 AM)

Part 1
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Abstract Information

Track Selection

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2nd choice: Environmental Health

Introduction

Despite increased screening and evolving awareness of lead exposure, the development of treatments for lead-exposed children has slowed substantially since the early 2000s. The CDC has progressively lowered the blood lead reference value for children from 60 µg/dL in the 1960s to 30 µg/dL in 1978, 25 µg/dL in 1985, 10 µg/dL in 1991, 5 µg/dL in 2012, and 3.5 µg/dL in 2021. These changes reflect evidence that harm occurs at the lowest detectable levels.

Since 1991, however, the blood lead level (BLL) at which chelation therapy is indicated has remained 45 µg/dL, and most guidelines recommend against using chelation therapy for BLLs < 45 µg/dL. A substantial treatment gap therefore exists for children with BLLs between 3.5 and 45 µg/dL, who have few medical options once exposed. This gap reflects an asymmetric application of evidence: chelation at very high BLLs is accepted despite the absence of modern randomized trials demonstrating neurocognitive benefit, whereas a single trial that failed to show benefit at lower BLLs has often been interpreted as evidence that chelation is ineffective throughout much of the 3.5–45 µg/dL range.

Current treatment guidelines rely heavily on findings from the Treatment of Lead-Exposed Children (TLC) randomized controlled trial, which evaluated the effects of succimer (DMSA) chelation on IQ in children with BLLs 20–44 µg/dL. The investigators showed that although succimer lowered BLLs in the short term, this effect was not sustained, and no cognitive benefit was detected after 3 years of follow-up. They also reported slightly reduced linear growth in the treatment group. They concluded that chelation therapy was not indicated for children with BLLs < 45 µg/dL and suggested that efforts should shift toward primary prevention and away from finding and treating patients.

In the years that followed, these conclusions were fundamental in shaping U.S. environmental health policy, shifting responsibility away from clinical treatment by physicians and toward housing and environmental interventions by federal and state agencies. While this shift has been beneficial in many ways, it has not prevented children from being exposed to lead hazards. As a result, many children continue to be exposed yet do not meet current thresholds for chelation. Until lead hazards are fully addressed, finding and treating children who have already been exposed remains necessary.

TLC was conducted prior to widespread adherence to CONSORT and ICMJE standards. Given its continued influence, we believe that a re-examination of the TLC trial is warranted. This poster will examine the trial's methodology, limitations, and impact on U.S. environmental health policy and clinical treatment guidelines over the last 25 years.

Methods

We performed searches on Google, Archive.org, ClinicalTrials.gov, NIH RePORTER, NIHRecord.NIH.gov, LexisNexis, CDC Stacks, and Accessdata.fda.gov for contemporaneous evidence surrounding the trial and approval of succimer. We accessed archived versions of the NIEHS website using the Wayback Machine to try to find earlier versions of the protocol and gain a better understanding of the background of the trial. We performed searches on EHP, Pediatrics, and Google Scholar using the following search terms: 'TLC', 'Treatment of Lead-Exposed Children', 'succimer', 'chelation', 'lead exposure', 'lead', 'Rogan'. We searched Web of Science, Scopus, Embase, and PubMed using the following terms: 'succimer', 'chelation', 'TLC', 'Treatment of Lead-Exposed Children'.

We conducted a retrospective mixed-methods appraisal of the TLC trial's design, conduct, analysis, and reporting. We performed a systematic appraisal of the TLC protocol and primary outcome publications using the SPIRIT and CONSORT expanded checklists. We read the full protocol and cross-referenced it with what was reported in the main TLC papers.

We used a mixed-methods approach and the Cochrane Risk-of-Bias 2 tool (RoB 2) to assess overall risk of bias.

Results

We located a 1997 version of the TLC protocol via archived NIEHS webpages and included 23 articles in our final review.

Major limitations included:

The environmental intervention was designed to suppress BLLs for only 6 months, and ancillary TLC reports suggest that ongoing exposure remained incompletely controlled. Investigators described the intervention as a "cleaning," not a comprehensive abatement, and many homes remained above EPA lead dust standards afterward.

The treatment target of 15 µg/dL was likely inadequate, as more recent evidence indicates the expected IQ gain from such a reduction (~10 µg/dL) would be too small for the trial to detect a minimal clinically important difference.

The trial did not monitor essential minerals such as iron, zinc, calcium, and copper, creating a risk that observed harms (e.g., decreased height) reflected unmeasured, chelation-induced nutrient deficiencies. These minerals are affected by lead exposure, are necessary for neurodevelopment, and their deficiency increases lead absorption. Iron deficiency also increases lead exposure via pica behavior. Investigators acknowledged that children in TLC were at high risk of mineral deficiency and that succimer could further deplete minerals. Although multivitamins were provided, adherence was highly variable. While succimer is less likely than other chelators to cause mineral deficiency, it was given for up to three 26-day courses, increasing the likelihood of unmeasured depletion.

Although baseline ferritin was measured, ferritin values were not used in decision-making, and baseline values were omitted in all but one paper (the 2006 growth report). In that instance, the arithmetic mean was used to describe baseline ferritin, although the geometric mean is generally a more appropriate measure of central tendency for right-skewed distributions such as ferritin. This likely overstated average iron stores and obscured how many children were close to deficiency at baseline.

Investigators inadvertently dispensed lead-contaminated multivitamins to many participants, including 149 siblings of participants, whom investigators had also encouraged to take the vitamins. Investigators published a report on the incident, which was cited in the primary outcome article, but was not cited or addressed as a limitation in subsequent publications on secondary outcomes. The interpretation of the incident was used to excuse any impact on outcomes, conflating the absence of evidence of a dose-response with evidence that a dose-response was absent.

Adherence was measured by electronic pill bottles at one site and parental report and/or pill counts at others.

Adherence measurements by trial site and by treatment group were not reported.

We found multiple instances of reporting inconsistencies.

Conclusion

The methodological limitations of the TLC trial should temper the conclusions that succimer is ineffective or harmful for children with BLLs < 45 µg/dL. These flaws may have biased the trial's findings toward the null and may have misattributed adverse effects to the chelation regimen rather than to correctable factors such as nutrient depletion. Given that lead is a known neurotoxin with no safe level of exposure, the wholesale abandonment of treatment in this range appears premature. New, well-designed pragmatic trials are needed.

Available clinical and safety data, including TLC, suggest that succimer is relatively safe and effective at lowering blood lead levels. Furthermore, because bone lead stores act as a long-term source of endogenous re-exposure, there is a coherent rationale for re-examining chelation as a therapeutic option in children with moderate BLLs.

Future trials should prioritize clinically meaningful outcomes and aim for post-treatment BLLs below the current 3.5 µg/dL reference value. This will require ongoing assessment, correction, and maintenance of mineral status, with exclusion or, at minimum, stratification of iron-deficient participants, and prespecified, transparent handling of off-protocol deviations. Trials should also clearly position themselves along the pragmatic–explanatory spectrum before protocols are finalized. TLC sought to answer a pragmatic question (long-term neurodevelopment) but did so in a narrowly defined population more consistent with an explanatory design, a mismatch that limited the inferences that could be drawn. Adopting clearly pragmatic or clearly explanatory designs, rather than blending elements of both, would yield clearer insight into the role of lead chelation in children.

Finally, future trials must ensure that environmental lead abatement is comprehensive and sustained, because chelation alone cannot maintain lower BLLs when exposure continues. Incorporating these design principles will be essential for generating credible evidence to guide the future role of chelation therapy in children with lead exposure.

Statement and Policy

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