Recent Recall of Iron Reagent—Investigation of Potential Reagent Contamination and Assay Improvement Strategy

Article:
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Guests: Drs. Alagar Muthukumar and Madhusudhanan Narasimhan from the University of Texas Southwestern Medical Center in Dallas, Texas.

Randye Kaye: Hello and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

In 2023, a major clinical chemistry assay manufacturer issued a recall of their iron reagent due to a high bias of iron results that were observed at some customer laboratory sites. Iron test results are often incorporated into other calculations to assess iron sufficiency, such as total iron binding capacity and transparent saturation. Therefore, the impact of inaccurate iron results could be significant. Affected laboratories were instructed to review the details of the recall with their medical director or laboratory management and to follow their laboratories protocol regarding the need for reviewing previously reported patient results.

The November 2024 issue of *JALM* features an article describing one clinical laboratory's investigation into the root cause of the high iron bias within the affected assay reagents. The investigation included spectral scan analysis and trace element analysis of the reagents. The authors' findings led them to propose a suspected contaminant that caused the bias, and they also demonstrated a technique to mitigate the bias. The author's findings may serve as a critical reminder to clinical laboratories of the importance of quality control and remaining vigilant to ensure accurate test results and patient safety.

Today, we're joined by two of the article's authors. Dr. Alagar Muthukumar is currently a medical director for the Clinical Chemistry Laboratories at the University of Texas Southwestern Medical Center. Dr. Kumar has over 15 years of experience in the diagnostics industry and the academic hospital setting and has research interests in assay improvement and test utilization. Dr. Madhusudhanan Narasimhan is currently a second-year clinical chemistry fellow at UT Southwestern. Dr. Narasimhan is also an accomplished laboratory scientist with over 20 years of

experience in leadership roles of funded research. Welcome, Madhu and Dr. Kumar.

A reagent recall is a clinical laboratorian's nightmare, but it is something that does happen sometimes. In general, what do you think are some reasons for product recalls for diagnostic products?

Madhusudhanan Narasimhan: Thank you for asking this question. There are several reasons why a product vendor can recall a reagent. So some of the common reasons that we see are manufacturing defects such as, you know, contamination during the manufacturing process or sometimes because of the cost or availability, they may replace one ingredient for another. So these are some of the common reasons. Besides that, sometimes there is also mislabeling issues or packaging issues. These are also some of the reasons for the reagent recall.

Randye Kaye: All right, thank you. So Madhu, in this case of an iron reagent recall, what are some specific concerns with this test in particular and how might falsely elevated iron results affect management and care of patients?

Madhusudhanan Narasimhan: Well, first, the affected lots in our case were found to potentially generate a false elevation in QC performance and also iron results in patient samples, with a positive bias of 15 to 30%. Secondly, at that point in time of recall, the reasons underlying this positive bias were unclear. In fact, several laboratories had already switched to the affected lots before the recall notice was received. Thirdly, no alternative working lots were made available and the field action letter left the next course of action to the lab directors, and also timeline for the availability of new lots of reagents were also not given. And this uncertainty left the customers with several operational related challenges as to how long they would have to wait for the new lots and how long they must arrange for alternative testing.

Apart from that, importantly, the iron test is often ordered in conjunction with ferritin, total iron binding capacity [TIBC], transferring saturation, and unbound iron binding capacity [UIBC] to diagnose iron deficiency anemia and iron metabolism disorders. The latter 3 indices, specifically TIBC, transferring saturation, and UIBC are derived results that uses iron values in their calculations.

Thus, if you see, the impact of inaccurate iron results can reflect beyond iron alone and can go on to offer the other three test results. So these incorrect diagnoses can divert attention from the actual underlying issue a patient may have. This can lead to unnecessary investigations, and at

times, unnecessary treatments such as iron chelation therapy, thinking that it could be an iron overload. So all these potentially can cause patient anxiety, stress, and misallocation of resources. And these are some of the problems that one could see because of false elevation in the test result here, you know, especially the iron assay in question.

In addition, these uncertainties caused delays in diagnosis and turnaround times for results as tests had to be sent out elsewhere that uses a different reagent and/or testing platforms. This situation not only caused anxiety, stress, and inconvenience for the patients and providers, but also can have broader implications for trust. While this issue may be seen as an accidental problem originating from the manufacturer, it can dent the confidence and trust of the patients have on healthcare providers, laboratory, and overall on certain testing strategies. In fact, some patients may become wary of the reliability of certain tests impacting their willingness to seek care.

Randye Kaye: Thank you. Yeah, that--those are very legitimate concerns. I'll direct the next question to you, Kumar. Your investigation led your group to a likely root cause of the high bias of iron in this reagent. So, can you share, what was this significant conclusion that you came to and how might reagent manufacturers avoid this type of issue in the future?

Alagar Muthukumar: Thank you, Randye, for asking this question. So most of the assays that we use in our lab are FDA approved assays and they are mostly robust and reliable. But sometimes manufacturers do voluntarily recall some reagents. So in this case, we investigated the recent recall of iron reagent and found out that there was a significant copper contamination in R2 reagent. We confirmed this using ICP-MS analysis.

After the confirmation, we also verified it by spiking copper into a good reagent that does not have copper contamination. So, once we confirmed the copper is the main source of the contamination, we also try to prevent the adverse impact of copper by adding a copper chelating agent, thiourea, into R2 reagents. So by adding copper and preventing the copper chelating with the iron reagent, we showed that copper is the main culprit in this reagent recall. And if you see 2023 survey shows that nearly 70% of the manufacturers are using the same ferene/ferrozine-based assay, suggesting that this kind of incident can happen to any manufacturer. So to prevent such incidents happening in the future, we recommend that a thiourea be added in the R2 reagent to prevent false increase in iron values due to copper or any other related metal contamination.

Randye Kaye: All right, thank you. You know, earlier this year in September 2024, there was a major study published in a different journal in *JAMA Network Open*, and that found an alarmingly high prevalence of iron deficiency in the US. And the article also pointed out limitations with the current screening strategies for iron deficiency. Can you share just a little bit more about this and how it underscores the importance of accessible and accurate laboratory testing?

Alagar Muthukumar: Thank you, Randye, for asking this very important question. Currently, CDC recommends screening for non-pregnant female adolescents and women every 5 to 10 years, but there is no such guidelines for screening or surveillance in general population. As you know, most of these studies have focused on this vulnerable population, such as, you know, pregnant women or teenage girls. So those studies had previously shown that there is a significant percentage of US population who are iron deficient. But the recent study that was published in *JAMA* focused on the general population. So in the general population, they showed that more than 14% of the adolescents and also adults had iron deficiency, both either absolute iron deficiency or functional iron deficiency.

So what they indicate is that if you are going by the CDC guidelines, more than, you know, 70% of this iron deficiency can be missed. So this is a very alarming finding. So the one way to, you know, strengthen this and improve access to testing is strengthening our guideline recommendations.

Randye Kaye: That is quite alarming. Thank you so much. One final question. I'll direct this to you, Madhu. Finally, going back to the issue of reagent recalls. So what advice do you have for clinical laboratories who get a recall notice from their reagent manufacturer? What steps should they take?

Madhusudhanan Narasimhan: Well, that's very important portion, you know. The first thing would be obviously to cease using the recalled assay and document the recall and any actions taken and further you review the recall notice and understand if there is any reason provided for the recall or any associated risks. Then you'll have to go back, review the records, determine if any of the patients have been tested with the recalled assay, and evaluate the clinical implications, that is, consider any potential impact of inaccurate results on patient care and management. Meanwhile, you'll have to communicate with the team and notify the staffs about the recall, its implications, the necessary actions to take, and ensure that they understand how to handle recall products and the importance of following protocols. And you'll have to also document the recall and any actions taken, and create a summary report for internal use and for regulatory compliance.

Finally, you'll have to communicate with the affected patients, discuss the need for retesting or further evaluation to ensure accurate diagnosis. Also, you have to coordinate with clinicians and work with them to manage any necessary follow-up for affected patients. And also in facilities like UT Southwestern that have multiple satellite centers, if you have an inventory for good working lots available, meanwhile we can sequester all the working lots from the different satellite centers and consolidate the testing in one location. This can be an effective strategy to minimize the reagent usage or wastage that can occur through QC testing and calibrations at each centers.

If such decisions are taken, it is crucial to communicate the plan of action to the clinical laboratory service management and caregivers. While this approach is not a permanent solution, it can buy you some time and serve as a practical stopgap arrangement. So in sum, react quickly, notify authorities, give an explanation, and be available for questions and offer refunds and retesting. So these are some of the things that you can immediately attend to following a recall notice.

Randye Kaye: All right, thank you. That's very important information and strategies. Thank you to both of you for the article and for joining us today.

That was Drs. Alagar Muthukumar and Madhusudhanan Narasimhan from the University of Texas Southwestern Medical Center discussing the *JALM* article, "Recent Recall of Iron Reagent—Investigation of Potential Reagent Contamination and Assay Improvement Strategy."

Thanks for tuning in to this episode of *JALM* Talk. See you next time and don't forget to submit something for us to talk about.