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Review Article

Interferences in Clinical Chemistry: A Neglected Cause of Laboratory Errors in Medical Practice in resource constrained settings

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Abstract

Interferences—endogenous and exogenous factors that distort analytical measurements remain an under-recognized source of laboratory error, particularly in low-resource settings. In Nigeria and Sub-Saharan Africa (SSA), persistent limitations in laboratory infrastructure, workforce training, and quality management systems exacerbate vulnerabilities across the total testing process and increase the risk of clinically significant errors. This review aimed to examine the types, mechanisms, frequency, and clinical impact of common analytical interferences in clinical chemistry, with particular emphasis on haemolysis, lipaemia, and icterus (HIL); to identify key drivers of interference-related errors in SSA; and to propose pragmatic mitigation strategies tailored to resource-limited laboratories.

A narrative review of peer-reviewed literature and authoritative laboratory guidelines was conducted using PubMed and PubMed Central up to November 26, 2025. Search terms included "haemolysis," "lipaemia," "icterus," "pre-analytical error," "interference," "clinical chemistry," "Nigeria," and "Africa." Priority was assigned to studies originating from SSA or those directly relevant to low-resource laboratory settings, as well as to international consensus and professional guidelines.

Haemolysis, lipaemia, and icterus were consistently identified as the most frequent endogenous interferences and major contributors to pre-analytical and analytical errors. A systematic review of African laboratories reported a pooled pre-analytical error prevalence of approximately 17.5% (95% CI: 11.6–23.5%), substantially exceeding rates commonly reported in high-income countries, with haemolysis being the leading cause of sample rejection and analytical error. Despite limited sensitivity, visual inspection remains the predominant method for interference detection in many SSA laboratories, whereas automated HIL indices and assay-specific rejection thresholds demonstrably improve detection, standardization, and clinical decision-making. Contributing factors include inadequate phlebotomy training, delayed specimen transport, absence of standardized rejection policies, and lack of local verification of manufacturer interference limits.

Interference-related errors in clinical chemistry are common, clinically significant, and frequently overlooked in SSA. Implementing targeted phlebotomy training, simple workflow improvements, adoption or verification of HIL indices, method-by-method interference validation, and participation in external quality assessment can substantially reduce error rates and enhance patient safety, even within constrained resources.

Keywords: haemolysis; lipaemia; icterus; pre-analytical errors; clinical chemistry; Sub-Saharan Africa; HIL indices; laboratory quality

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Introduction

Accurate clinical chemistry results underpin critical decisions for diagnosis, management, and monitoring of patients. The reliability of these results is contingent not only on well-performing analytical methods, but also on integrity throughout the pre-analytical, analytical, and post-analytical phases. Among the threats to result validity, interferences — defined as endogenous (e.g., haemolysis, lipaemia, elevated bilirubin, paraproteins) or exogenous (e.g., drugs, heterophile antibodies) factors that distort measurement — remain pervasive yet frequently under-appreciated [2–4].

In high-income settings, laboratories invest in automated interference detection, validated rejection criteria, and robust quality assurance systems. By contrast, many laboratories in Sub-Saharan Africa (SSA) operate under constrained resources, depend on visual sample inspection, and frequently lack verified assay-specific interference thresholds. In such circumstances, interference-related errors may persist unchecked, compromising patient care and undermining clinician confidence in laboratory data. This review seeks to: (1) elucidate the common types and mechanisms of analytical interferences in clinical chemistry; (2) review evidence for their prevalence and impact in resource-constrained Nigeria and SSA; and (3) propose practical, resource-appropriate mitigation strategies for laboratories in these areas.

Methodology

A comprehensive literature review was conducted on clinical interference with particular reference to hemolysis, lipemia, and icterus using electronic databases including PubMed, Google Scholar, Scopus, and laboratory standards documents. Only peer-reviewed papers on the subject of reference were considered. Unrelated and duplicate materials were excluded. The three authors reviewed and selected relevant articles to be included or removed in the course of review. The extracted data were then analyzed and discussed using a narrative synthesis. The findings from these studies were categorized based on the study objective and presented as documented in the sections below.

Types and Mechanisms of Analytical Interference

Endogenous interferences

Haemolysis: In vitro (or rarely in vivo) rupture of red blood cells releases intracellular constituents — such as potassium, lactate dehydrogenase, aspartate aminotransferase, and free hemoglobin — which may cause falsely elevated or diluted results. Free hemoglobin also absorbs broadly across wavelengths used in photometric assays, causing spectral interference or direct reagent interaction [2,8].

Lipaemia: Turbidity from chylomicrons or very low-density lipoproteins in serum/plasma scatters light in spectrophotometric assays, producing spurious increases or decreases in analyte readings depending on the assay design. Additionally, volume displacement by lipids may alter analyte concentration expressed per volume of serum/plasma [4,9].

Icterus (hyperbilirubinaemia): Elevated conjugated or unconjugated bilirubin can absorb at measurement wavelengths or react directly with reagents, thus interfering with colorimetric or enzymatic assays [2,10].

Other interferences: Paraproteinaemia, due to monoclonal immunoglobulins may change sample viscosity or cause precipitation, affecting immunoassays or other analytical methods. Exogenous compounds (medications, contrast agents) and heterophile antibodies may cause assay-specific biases, particularly in immunoassays [11,12].

Exogenous interferences

Exogenous interferences in laboratory testing are increasingly recognized as a significant challenge to accurate clinical decision-making in Nigeria and across Sub-Saharan Africa. These analytical disruptions arise from external substances introduced into the patient's circulation or sample matrix, and are frequently overlooked causes of laboratory error. Common sources include medications such as antiretrovirals, antibiotics, and chemotherapeutic agents, which may alter analyte concentration or interfere with assay chemistry.[13] The widespread use of herbal and traditional remedies often with undocumented pharmacologic properties, further contributes to unpredictable assay behaviour.[14]

Additionally, contamination from disinfectants and skincare products during sample collection can alter spectrophotometric measurements or introduce inhibitory substances.[9] Intravenous infusions, including parenteral nutrition, lipid emulsions, and glucose-containing fluids, may lead to sample dilution or cause turbidity that affects photometric methods.[15] Diagnostic imaging contrast media, particularly iodinated and gadolinium-based agents, have been documented to interfere with creatinine assays and immunoassays.[16] Given the high burden of infectious and chronic diseases in the region, such interferences are frequently encountered yet under-reported.

Mitigation requires a high index of suspicion from the Chemical Pathologist, including review of medication history, inquiry about herbal use, and direct communication with clinicians to understand pre-analytical conditions. Strengthening patient preparation protocols and applying analytical safeguards such as delta checks and alternative methodologies when interference is suspected, are essential steps toward improving result reliability. Ultimately, heightened awareness and implementation of standardized interference management strategies will enhance diagnostic accuracy and patient safety in resource-limited settings.

Mechanisms of interference

Interferences produce biases through diverse mechanisms: optical (spectral overlap or scattering), chemical (direct reaction with reagents), physical (matrix effects such as viscosity/turbidity, volume displacement), and dilutional artifacts (from cell lysis). The net effect, magnitude and direction of bias is analyte- and method-specific, underscoring the necessity for method-by-method verification [2,9].

Prevalence and Impact of Interference-Related Errors in SSA

Laboratory error studies in SSA suggest that pre-analytical and interference-related problems are common. A meta-analysis encompassing 19 studies from African laboratories reported a pooled pre-analytical error prevalence of 17.5% (95% CI: 11.6–23.5%) markedly higher than rates reported in many high-income regions [1]. In these studies, haemolysis was frequently cited as the leading cause of specimen rejection or sample unacceptability [1–3].

Retrospective data from a tertiary hospital in South Africa, examining over 10,000 lipid profile specimens, reported that 15.3% had at least one interference: lipaemia in 13.9%, haemolysis in 1.17%, and icterus in 0.25%. The presence of interference significantly distorted lipid and lipoprotein measurements compared with clear samples [4].

Comparative assessments between visual inspection and instrument-based serum indices reveal poor concordance: in a cohort of 1,509 serum samples, automated detection identified a substantial proportion of haemolysed, lipaemic, and icteric specimens that were missed by visual screening; inter-observer agreement for visual inspection was low (kappa coefficients: 0.19 for haemolysis, 0.34 for icterus, 0.13 for lipaemia) [5].

Beyond analytical distortion, interference-related errors have concrete clinical implications. For example, hemolysis can cause spurious hyperkalaemia, precipitating inappropriate management; lipaemia or bilirubin interference may mask or mimic liver dysfunction; and distorted creatinine values can mislead renal function assessment [2,4,9]. A recent multicentre verification study on a modern chemistry analyzer demonstrated that of 35 routine assays, 12 were significantly affected by haemolysis, four by bilirubin, and three by lipaemia — further emphasizing the pervasiveness of this problem and the need for assay-specific interference thresholds [6].

Amplifying Factors in SSA Laboratories

Several systemic and contextual factors in SSA amplify the risk and impact of interference-related errors:

1. Inadequate phlebotomy training and practice: Blood collection is frequently performed by non-specialist staff lacking formal phlebotomy training; use of small-bore needles, forceful aspiration, prolonged tourniquet application, and improper mixing increases in vitro haemolysis [6,17].

2. Delayed specimen transport and processing: Long distances, suboptimal courier systems, lack of temperature control, and prolonged transport in tropical climates contribute to red cell fragility, lipid instability, and bilirubin degradation [6,18].

3. Reliance on visual sample inspection: Many laboratories lack analysers with serum-index capability; visual assessment remains the default for HIL detection despite its subjectivity, insensitivity to mild-to-moderate interference, and poor reproducibility [2,3,9].

4. Absence of local verification and standardised rejection policies: Manufacturer-provided interference thresholds are often not locally verified; in the absence of formal standard operating procedures (SOPs), rejection or reporting practices vary widely, potentially resulting in inconsistent or unsafe reporting [8,17].

5. Resource constraints limiting mitigation strategies: Techniques such as ultracentrifugation to clear lipaemia, sample dilution, or alternative assay methods may be unavailable or too costly; repeat sampling may be impractical due to patient factors or clinician resistance [18].

6. High disease burden and patient mix: SSA has a high prevalence of conditions associated with hyperbilirubinaemia, lipaemia, or paraproteinaemia (e.g., neonatal jaundice, malnutrition, infections, chronic liver disease); frequent paediatric and neonatal testing further increases susceptibility to interference [7,19].

Mitigation Strategies — Practical Recommendations for Laboratories

Given resource constraints, many effective mitigation measures are low-cost and immediately implementable. A tiered strategy is proposed:

Short-term, low-cost interventions

Phlebotomy training and competency certification: All personnel drawing blood should receive standardized training in phlebotomy technique (appropriate needle size, gentle aspiration, minimizing tourniquet time, and correct tube mixing). Periodic audits of haemolysis rates should be implemented to monitor performance [6,17].

Standard operating procedures (SOPs) and analyte-specific rejection/comment policies: Even a simple table listing common analytes with known interference risk and the appropriate response (reject / comment / repeat/accept with caution) improves consistency and safety [8].

Optimized specimen handling and transport: Prompt centrifugation after collection, gentle handling during transport, use of cool boxes where available, and prioritization of rapid processing help minimize in vitro haemolysis and sample degradation [18].

Use of visual aids and documentation: For laboratories without instrument-based HIL indices, implement standardized colour/turbidity charts or photographic guides; record all suspect specimens to monitor frequency over time and identify trends requiring intervention [2].

Medium-term / Moderate-cost interventions

Adoption of analyzers with HIL-index capability (when procuring equipment): Preference should be given to platforms that provide objective HIL indices. On installation, laboratories should verify manufacturer interference thresholds for each analyte before clinical use [8,17].

Assay-by-assay interference verification: For critical analytes (e.g., electrolytes, renal/liver function tests, lipids), laboratories should perform local interference studies for example, spiking clean serum/plasma with hemolysate, lipemic serum, or bilirubin, to define clinically acceptable cut-offs specific to their population and methods [9,12].

Alternative lipaemia management: In the absence of ultracentrifuges, high-speed centrifugation, validated dilution protocols, or use of non-spectrophotometric assay methods may reduce lipaemic bias, but each must be locally validated for analyte stability and accuracy [18].

Long-term / System-level improvements

Implementation of quality management systems and participation in external quality assessment (EQA): Laboratories should aim to adopt recognized quality frameworks (e.g., ISO 15189), monitor key quality indicators (e.g., hemolysis rate, sample rejection rate, turnaround time), and enroll in EQA/proficiency testing schemes to benchmark against peers [5,21].

Procurement policies prioritizing quality-assured platforms: Hospital and regional procurement committees should favor analyzers with robust interference detection, manufacturer support for method verification, and maintenance capacity.

Clinical–laboratory communication and result comment policies: Regular multidisciplinary meetings and standardized comment templates (e.g., "Sample flagged as haemolysed; result may be inaccurate; repeat sampling recommended") will enhance clinician awareness and support safe interpretation of flagged or rejected results.

Limitations and Gaps in the Evidence

This review was constrained by the limited quantity of peer-reviewed studies that explicitly quantify interference-related clinical errors in SSA. Most published data describe pre-analytical error broadly, rather than analyte-specific interference outcomes. There is a paucity of prospective, multicenter studies linking interference detection and mitigation strategies to clinical outcomes (misdiagnosis, adverse events, cost savings). Furthermore, most available data derive from tertiary or reference laboratories, limiting generalizability to smaller, peripheral, or primary care laboratories. Additional research is required to: (a) quantify incidence and types of interference across varied SSA settings; (b) evaluate effectiveness and cost-effectiveness of mitigation strategies; (c) develop and validate local interference thresholds; and (d) assess clinical impact of improved interference management.

Recommendations

!. Multicenter and multidisciplinary studies are encouraged to conduct research on exogenous and endogenous interferences, which often cross-react with assays in resource-constrained climes

Results

Across SSA, interference-related errors were reported predominantly within the pre-analytical phase. A systematic review and meta-analysis of 19 African studies reported a pooled pre-analytical error prevalence of 17.5% (95% CI: 11.6–23.5%), substantially exceeding rates typically reported in high-income settings [1]. Haemolysis was consistently identified as the most frequent cause of specimen rejection and analytical interference [1–3].

Institutional studies demonstrated wide variability in interference prevalence depending on patient population, analyte profile, and detection method. In a large retrospective South African study of over 10,000 lipid profile samples, 15.3% exhibited at least one form of interference, with lipaemia (13.9%) being most frequent, followed by haemolysis (1.17%) and icterus (0.25%) [4].

Distribution of Common Endogenous Interferences

Haemolysis emerged as the predominant endogenous interference across multiple studies, particularly affecting potassium, lactate dehydrogenase, aminotransferases, and phosphate assays. Lipaemia was frequently encountered in lipid profiles and routine chemistry panels, especially in non-fasting patients and those receiving lipid-containing infusions. Icterus occurred less frequently overall but was clinically significant in neonatal, hepatic, and haemolytic disease contexts [2,4,7].

Detection Methods and Laboratory Practices

Visual inspection remained the most common method for detecting HIL interferences in SSA laboratories. However, comparative studies demonstrated poor concordance between visual assessment and automated serum indices. In one study involving 1,509 serum samples, automated HIL detection identified a substantial number of haemolysed, lipaemic, and icteric specimens that were missed by visual inspection. Inter-observer agreement for visual detection was low, with kappa values of 0.19 for haemolysis, 0.34 for icterus, and 0.13 for lipaemia [5].

Analytical Impact Across Assays

Assay-specific vulnerability to interference was well documented. A multicenter verification study evaluating 35 routine chemistry assays found that 12 assays were significantly affected by haemolysis, four by bilirubin, and three by lipaemia at clinically relevant concentrations [6]. The magnitude and direction of interference varied by analytical method, confirming the necessity for assay-specific interference thresholds.

Tables

Table 1: Reported Prevalence of Pre-Analytical and Interference-Related Errors in SSA

Study / Setting	Study Design	Sample Size	Key Findings
Asmelash et al., 2020 [1]	Systematic review & meta-analysis	19 studies	Pooled pre-analytical error rate: 17.5% (95% CI: 11.6–23.5%); haemolysis most frequent
Degfe et al., 2023 [5]	Cross-sectional audit (Ethiopia)	1,509 samples	High burden of undetected HIL using visual inspection
Magwete et al., 2018 [4]	Retrospective review (South Africa)	>10,000 samples	15.3% with ≥1 interference; lipaemia predominant

Table 2: Common Endogenous Interferences and Affected Analytes

Interference	Primary Mechanism	Commonly Affected Analytes	Clinical Impact
Haemolysis	Optical & dilutional	Potassium, LDH, AST, ALT, phosphate	Pseudohyperkalaemia, false enzyme elevation
Lipaemia	Light scattering, volume displacement	Lipids, glucose, sodium, and liver enzymes	Masked dyslipidaemia or spurious abnormalities
Icterus	Spectral overlap, chemical interaction	Creatinine, total protein, enzymes	Misclassification of hepatic or renal function

Table 3: Comparison of Visual Inspection and Automated HIL Detection

Detection Method	Advantages	Limitations	Evidence
Visual inspection	Low cost, universally available	Subjective, poor sensitivity, low reproducibility	Low kappa values reported [5]
Automated HIL indices	Objective, assay-linked thresholds	Requires compatible analyzers	Improved detection and decision-making [4–6]

Table 4: Systemic Factors Amplifying Interference Risk in SSA Laboratories

Factor	Effect on Interference	References
Inadequate phlebotomy training	Increased in vitro haemolysis	[6,17]
Delayed transport & processing	Sample degradation, lipaemia instability	[18]
Lack of SOPs and local verification	Inconsistent reporting/rejection	[8,17]
Resource limitations	Limited mitigation options	[18]

Conclusion

Interferences, particularly haemolysis, lipaemia, and icterus, remain a common, under-recognized source of error in clinical chemistry laboratories across Sub-Saharan Africa. Given the widespread resource constraints, reliance on visual sample inspection, and absence of standardized rejection policies, the risk of erroneous results is substantial. However, many effective mitigation strategies are low-cost, feasible, and can be implemented without a major infrastructural overhaul. Prioritizing phlebotomy training, standard operating procedures, adoption or verification of HIL indices, method-specific interference validation, and quality assurance will significantly enhance the reliability of laboratory results, clinician confidence, and ultimately patient safety. This should be a strategic priority for laboratory managers, hospital administrators, and public health policy makers in Nigeria and SSA.

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