**Title:** Exploring new diagnostic approaches for Buruli ulcer disease

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**Background:** Buruli ulcer, a neglected tropical disease caused by *Mycobacterium ulcerans*, remains a significant health concern primarily in sub-Saharan Africa, though sporadic cases have been documented worldwide. This disease is characterized by painless skin nodules that expand into deep ulcerations, with the lipid toxin mycolactone playing a pivotal role in its pathogenesis. Despite its global impact, diagnostic tools for Buruli ulcer remain inadequate. Currently, polymerase chain reaction (PCR) is the gold standard method for diagnostic confirmation, with over 70% of the cases reported to the World Health Organization based on PCR results. The main objective was to assess the limitations of PCR and to explore an alternative diagnostic approach utilizing mycolactone levels measured via enzyme-linked immunosorbent assay (ELISA). This study explored the correlation between mycolactone levels and clinical presentations in those with Buruli ulcer.

**Methods:** Biological specimens were collected from suspected Buruli ulcer patients at a clinic in Côte d'Ivoire. Clinical images and expert clinical disease likelihood scores were then analyzed alongside culture, PCR, and ELISA results.

**Results:** A total of 32 patients with Buruli ulcer lesions had positive ELISA results. Among these, 25% had negative PCR and culture results. Mycolactone levels in these patients exhibited a wide range (0.7-1810.9 ng; median = 4.9 ng), with corresponding variations in disease severity.

**Conclusions:** This study challenges the reliability of PCR as a sole diagnostic tool for Buruli ulcer and underscores the need for further investigations into alternative diagnostic modalities. ELISA-based mycolactone measurement emerges as a promising avenue to improve diagnostic accuracy. An increased understanding of the relationship between mycolactone levels and clinical presentation of Buruli ulcer can aid in early detection and management, going towards efforts to reduce the burden of disease.