Non-invasive screening for meningitis via high-frequency transfontenellar ultrasound: Results from the UNITED-Meningitis study in Mozambique

Muhammad Sidat¹, Beatrice M. Jobst², Sara Ajanovic²,³, Fabião Santos², Frances Carandel², Rita Quesada², Dulce Graça⁴, Paula Rodrigues⁴, Sebastião Ngovene⁵, Mastalina Zandamelá⁵, Justina Bramugy⁶, Pio Vitorino⁶, Janeta Machai⁵, Nilsa Nhatsave⁵, Anêliso Cossa⁵, Campos Mucasse⁵, Hassan Sial⁶, Paula Petrone⁶, W. Chris Buck⁴,⁷, Javier Jiménez², Quique Bassat⁸,⁹,¹⁰

¹ Faculdade de Medicina, Universidade Eduardo Mondlane, Maputo, Mozambique; ² Kriba, Barcelona Science Park, Barcelona, Spain; ³ Barcelona Institute for Global Health, Hospital Clinic de Barcelona, Barcelona, Spain; ⁴ Hospital Central de Maputo, Maputo, Mozambique; ⁵ Centro de Investigação em Saúde de Maniça, Maputo, Mozambique; ⁶ Biomedical Data Science Team, Barcelona Institute for Global Health, Barcelona, Spain; ⁷ University of California David Geffen School of Medicine, Los Angeles, USA; ⁸ ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain; ⁹ Pediatrics Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues, Barcelona, Spain; ¹⁰ Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

### Background

- Neonatal and infant meningitis is a life-threatening disease, with significant risk of death or permanent neurologic disability.
- Analysis of cerebrospinal fluid (CSF) obtained through lumbar punctures (LP) continues to be the gold standard for diagnosing meningitis.
- In resource-limited settings, conditions may not allow LP to be performed or CSF to be analysed for white blood cells (WBC).
- Alternative screening tools could help overcome this obstacle by detecting at-risk infants who may benefit from presumptive treatment and/or early referral.
- UNITED-Meningitis is a prospective diagnostic study evaluating a novel non-invasive, high-frequency ultrasonography (HFUS) exam for transfontanellar imaging using deep learning (DL) models for the detection of very low concentrations of WBCs in CSF.

### Methods

- Neonates and infants hospitalized at Hospital Central de Maputo with suspected meningitis (with/without pre-LP antibiotics) and an open anterior fontanelle were eligible for inclusion after informed consent.
- Known hydrocephalus and central nervous system malformations were exclusion criteria.
- LP was performed with CSF testing for cell counts, protein, and bacteriological exams (culture and latex agglutination).
- HFUS was performed at recruitment, with follow-up exams for participants with elevated WBC counts.
- HFUS images were processed by the DL algorithm, previously trained using a cohort of Spanish neonatal patients, and a threshold of ≥30 WBC/µL to define meningitis cases.

### Results

- Interim results analysis for 68 participants recruited from March 2021-June 2023 was performed.
- Exclusion of 2 participants diagnosed with hydrocephalus, 12 with inadequate image acquisitions (incorrect imaging location, excessive movement, overlying blood vessels, or poor coupling), 11 without CSF results and 24 with sub-optimal acquisitions (due to signal attenuation), 19 (27.9%) participants with 20 paired CSF WBC count/HFUS were included (one participant with a repeat LP during treatment).
- The DL algorithm correctly identified 5/5 meningitis cases (100% sensitivity) and 13/15 controls (86.6% specificity).

### Conclusions

- HFUS+DL show promise as a non-invasive, quick screening tool for CSF pleocytosis suggestive of meningitis in neonates and infants.
- Efforts are underway to improve HFUS image quality and penetration by using methods for improved coupling for patients with dense/curly hair or thicker fontanelles, higher voltage, increased pulse frequency, and refined DL models.
- Follow-up images will be analyzed to assess the use of HFUS+DL to measure treatment response.

---

**Image classifications**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>WBC number (cells/µL)</th>
<th>Classification Probability (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0-25 (median: 0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Meningitis</td>
<td>175-19200 (median: 380)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Deep Learning Model**

- HFUS+DL show promise as a non-invasive, quick screening tool for CSF pleocytosis suggestive of meningitis in neonates and infants.
- Efforts are underway to improve HFUS image quality and penetration by using methods for improved coupling for patients with dense/curly hair or thicker fontanelles, higher voltage, increased pulse frequency, and refined DL models.
- Follow-up images will be analyzed to assess the use of HFUS+DL to measure treatment response.