Global Normal Biological Ranges and Clinical Research in Africa?

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A cloud over my head
Normal Ranges

• These are accepted values for specific biological parameters used to guide:
  – Health status of persons
  – Clinical care
  – Classification of Adverse events
  – Determination of study end points
Normal Ranges

Sources of Data

• Surveys
• Clinical trials
• Routine check ups
• Pre-trial population evaluation

Drivers

• Clinical trials
• Development of regulatory framework
• Optimized clinical care
• Monitoring the evolution of physiological systems
Parameters

Common Variables
- Haematological
- Biochemical
  - Liver functions, renal, blood gases
- Immunological
  - CD4, CD8, IGg
- Spirometry
- Anthropometric
  - WT, Ht,
- Cardiovascular
  - ECG, cardiac output

Possible Confounders
- Age of the participants
- Time the samples were obtained
  - Temporal and spatial
- Physiological status
- Pooled data
- Genetic constitution of target population
African Context

• Few studies have looked at normal ranges

• Most are linked to clinical trials

• None are longitudinal

• Age bands are not wide enough for specific areas
## Males

<table>
<thead>
<tr>
<th>Site</th>
<th>Hb g/dl</th>
<th>Plt</th>
<th>wbc</th>
<th>Neutrophils %</th>
<th>Lymphocytes %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kintampo</td>
<td>13.9</td>
<td>88–352</td>
<td>5.5</td>
<td>48.6</td>
<td>41</td>
</tr>
<tr>
<td>Siaya</td>
<td>14.2 (11.4–16.9)</td>
<td>201 (102–307)</td>
<td>5.3 (2.5–7.4)</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Kericho</td>
<td>9.9 (8.3–11.3)</td>
<td>(115–366)</td>
<td>4.9 (3.0–9.1)</td>
<td>42 (20–70)</td>
<td>45 (20–60)</td>
</tr>
<tr>
<td>USA</td>
<td>13.5-17.5</td>
<td>103- 390</td>
<td>3.3-9.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcome

• The results obtained from the Kintampo area demonstrated that the red blood cell parameters (haemoglobin, haematocrit and RBC counts) were lower than values set as standards on the clinical haematology machines being used for clinical trials assessments in the study area.

• Significant gender differences were documented for the RBC parameters (haemoglobin, haematocrit and RBC),
Comparison to Reference values

- Out of range values for haematology ranged between 13 and 96% with parameters such as Haemoglobin, Haematocrit, RBC, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC) and white blood cell (WBC) predominantly on the lower side of the comparison values (Kintampo).
- OOR (22.5–35%) - for WBC, neutrophil, HB, HCT and platelet counts based on MGH US population-derived values in Siaya.
Kintampo

• OOR values for biochemistry were high for Amylase (28% and 18%), CK (74% and 58%), lactate dehydrogenase (LDH) (37% and 28%), Protein (34% and 31%), Total Bilirubin (23%), Urea (25% and 32%), Uric Acid (30% and 36%) and Phosphorus (23% and 24%) for males and females, respectively
• Young adults having higher levels of HB, HCT, RBC, and PLT as compared to adolescents

• Platelet counts were significantly higher among young adult females compared to the males in the same age group and also differed between adolescent and young adult males

• Young adult men and women did have higher values for creatinine and blood urea nitrogen compared to adolescent males and females, respectively.
Dichotomy

• Values for HB and MCV for both young adults and adolescents in Siaya were higher than those reported from another study in Kericho, Kenya but were slightly lower than those derived from Ethiopia, Kampala in Uganda and Mbeya in Tanzania

• Over 40% of our otherwise healthy study participants would have erroneously been considered to have at least one laboratory-based grade 1–4 toxicity adverse event (AE)
Key elements

• High eosinophil and low WBC and neutrophil values compared to those in North America
• Total bilirubin higher in African studies
• There was less variability in CD4 cell counts CD4CD8 ratio across centres and age groups
• It is difficult to develop consensus values across sites for a number of analytes
What next

• The development of region/age/gender specific reference values is thus essential to guide good conduct of clinical research

• These parameters are likely to change with time

• Trust the site clinical trial team
We are the same but very different
Go for the low hanging fruits

Each Study is unique
THANK YOU