RHEUMATIC HEART DISEASE IN UGANDA: RESEARCH TO CLINICAL PRACTICE

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ACKNOWLEDGEMENTS

• Partners: UHI, CNHS, GOLI, RHEACH
• Colleagues at UHI:
  • Emmy Okello, Isaac Sinabulya
• Nurses
• Support groups
• RHD Patients
UGANDA

- Estimated Population 44 Million
- Population Growth Rate 3.03%
- Total Fertility Rate 5.4 per woman
- Poverty Prevalence of 21.4%
- GDP Per Capita $706 (2017)
• Under-5 Mortality Rate 43 per 1,000 live births
• 54.7% of the population <18 years
• 33.4% Aged 6-17 years
• 75.2% of population <30 years
• Dependency ratio of 103%
• No National Health Insurance
NATURAL HISTORY OF RHD

Group A Streptococcal Infection

Inappropriate immune response

Carditis

Recurrent episodes of Acute Rheumatic Fever

Rheumatic Heart Disease

Group A Streptococci
e.g. Streptococcal pharyngitis ("Strep throat")

Acute Rheumatic Fever

Rheumatic Mitral Stenosis
Global burden of RHD, 2017

- >39 million persons living with RHD
- 80% in LMIC
<table>
<thead>
<tr>
<th>Tertiary Prevention</th>
<th>Secondary Prevention</th>
<th>Primary Prevention</th>
<th>Baseline Health Systems</th>
<th>Burden of Disease Data</th>
<th>RF/RHD Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Management</td>
<td>Anticoagulation</td>
<td>Triage and Preoperative Plan</td>
<td>Postoperative Planning</td>
<td>Cardiac Cath</td>
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</tr>
<tr>
<td>RHD/RF Register</td>
<td>BPG and other antibiotic supply</td>
<td>Provision of 2\textsuperscript{nd} prophylaxis</td>
<td>Priority based follow-up</td>
<td>Active case finding (echo)</td>
<td></td>
</tr>
<tr>
<td>Community Education</td>
<td>Sore throat dx + guidelines</td>
<td>Provision of Primary Prophx</td>
<td>Active case finding (ST clinic)</td>
<td>Vaccine development</td>
<td></td>
</tr>
<tr>
<td>Government Engagement</td>
<td>Disease notification</td>
<td>Human Resources</td>
<td>Health worker Training</td>
<td>Program evaluation</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td>Integration with healthcare system</td>
<td></td>
</tr>
</tbody>
</table>

**Research**

- Poverty
- Overcrowding
- Malnutrition
- Access to Healthcare

**TIPS CONCEPTUAL FRAMEWORK**

- **Baseline Health Systems**
  - Disease notification
  - Human Resources
  - Health worker Training
  - Funding
  - Lab services
  - Integration with healthcare system

- **Primary Prevention**
  - Government Engagement
  - Sore throat dx + guidelines
  - Provision of Primary Prophx
  - Active case finding (ST clinic)

- **Secondary Prevention**
  - RHD/RF Register
  - BPG and other antibiotic supply
  - Provision of 2\textsuperscript{nd} prophylaxis
  - Priority based follow-up
  - Active case finding (echo)

- **Tertiary Prevention**
  - Medical Management
  - Anticoagulation
  - Triage and Preoperative Plan
  - Postoperative Planning
  - Cardiac Cath
REFOCUSING ON RHEUMATIC HEART DISEASE

2010 and beyond

• Research begins to quantify what is felt by frontline healthcare providers across Uganda

• UHI develops a paper RHD registry UHI

• UHI makes a conscious decision to refocus on reducing the national burden of RHD

• RF/RHD committee formed within UHI
DISEASE BURDEN

- 4,869 Kampala School children aged 5-16 years underwent echo screening
- 2.7% had abnormal echo cardiograms
- Prevalence of 1.5% of RHD (72/4869 cases)
- 98% involvement of Mitral valve
- Lower socioeconomic groups had more prevalence of RHD and More advanced disease

Beaton et al, 2010
BURDEN OF RHEUMATIC HEART DISEASE: SCHOOL CHILDREN

- Over 15,000 children screened in Kampala (central), Mbarara (West), and Gulu (North) Districts

- **Pooled RHD prevalence 2.97% (95% CI 2.70-3.24%)** for latent RHD (echo detected)

- 2/3 borderline and 1/3 definite (screening vs. active case finding)

- **Upto 150,000 school age children have definite RHD**

- Some regional variability
  - Kampala 1.5% Vs Gulu 3.7%

BURDEN OF RHEUMATIC HEART DISEASE: COMMUNITY STUDY IN GULU

- 480 households screened (aged 5-50)
- 2,453 echocardiograms performed
- 2.5% children (37/1472) with RHD
- 2.3% adults (23/981) with RHD
- RHD prevalence of 13 per 1000 persons aged 5-60 years
- Prevalence increases with age, peaking at 16-20 years
  - Scheel et al, 2018
BURDEN OF RHEUMATIC HEART DISEASE: PREGNANCY OUTCOMES

- Prospective Screening echo in 3506 women, routine ANC, 2 rural HClIIs and 1 regional referral hospital over 24 months; Heart disease present in 58
- 17 per 1000 women with heart disease; 15 per 1000 of these (>85%) RHD
- Only 2 (3.4%) women had prior diagnosis
- CV complications occurred in 51% of women with heart disease, most commonly heart failure
- Only 1 maternal death – "best case" scenario, access to diagnosis, cardio-obstetrical consultation and care
- Population percent attributable risk of heart disease on maternal mortality 11%; fetal mortality 1.1% and Neonatal mortality 6%

Beaton et al, 2018
GENETICS OF RHD IN UGANDA

- 199 subjects; 96 RHD cases vs 103 controls aged 5-60 years
- HLA typing done and HLA-DR frequency comparison between cases and controls
- HLA-DR11 associated with increased risk of RHD (OR=331, P=<0.001, Pc<0.001)
- HLA-DR1 decreased risk of RHD (OR 0.42, P=0.01, Pc=0.09)

Okello et al, 2014
INCREASED FAMILIAL RISK

- All first degree relatives ≥5 years
  60 RHD cases/67 RHD negative controls
- 455/668 (68%) relatives screened
- Definite RHD more common among siblings of RHD positive cases
- RHD positive cases were 4.5 times more likely to have a sibling with RHD

Aliku et al, 2016
BURDEN OF RHEUMATIC HEART DISEASE: PRESENTATION AT TERTIARY CENTRE

1. Poor Health System infrastructure for early diagnosis and Referral
2. Patients present late with advanced RHD
   • 85% of patient with advanced RHD
   • 75% meet criteria for surgical or catheter-based intervention

Zhang et al, 2015
CLINICAL PRESENTATION

• 309 Patients aged 15-60 years
• Newly diagnosed RHD
• Complications such as CHF, PAH, Atrial Fibrillation, ARF recurrence, infective endocarditis, stroke
• Complications present in 49% (152/309)
• Heart failure: 46.9%, Atrial fibrillation 13.9%

Okello et al, 2013
Paediatric RHD at tertiary care

- 3503 abnormal echo reports of children <15 years from 2007-2011 At UHI
- CHD in 2,677;
- 826 had Acquired Heart Disease; RHD=376 (45.5%), DCMP 22.4%, Pericarditis 8.8%, EMF 7.1%
- MR in 98.9%, severe in 73%
- Mitral stenosis in 10.6%

Lubega et al, 2013
- 449 subjects aged 4-60 years followed at least for one year
- High one year Mortality 17.8%
- Most deaths within first three months of initial Presentation
- Predictors of mortality: Poor penicillin adherence, Heart failure, Advanced Disease (LVEDd>55mm)

Okello et al, 2013
BPG ADHERENCE

• 95 Patients (Aged 5-60 years) followed up for 6 months
• ≥80% Adherence: 54%
• Higher educational status and residence near health facilities favor good adherence
• Painful injections listed as main reason for none adherence
• Musoke et al, 2013
Quantifying and Addressing GAS

- Overall GAS Carriage of 15.9% (95% CI 12.8-19.5%),
- Pilot data shows 60% of children had at least 1 sore throat over 4 weeks, 41% of kids had a GAS pharyngitis
- Mild presentation (mean pain score 2.2)
- Consideration of reintroduction of pharyngitis into the IMCI
- AFROStrep: Collaborative multicenter study aimed at understanding the clinical, microbiological, epidemiological, and molecular characteristics of GAS in Africa
  Beaton et al, 2019
Table 3: Susceptibility rates of GAS Causing Acute Sore Throat\textsuperscript{14, 16}

<table>
<thead>
<tr>
<th>ANTIBIOTICS</th>
<th>MEAN VALUES ± SD</th>
<th>Resistant (%)</th>
<th>Indeterminate (%)</th>
<th>Susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lactams (mm)</td>
<td></td>
<td></td>
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<tr>
<td>Penicillin G</td>
<td>30.0 ± 2.7</td>
<td>0</td>
<td>0</td>
<td>68 (100%)</td>
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<tr>
<td>Ceftriaxone</td>
<td>27.3 ± 2.5</td>
<td>2 (2.9%)</td>
<td>2 (2.9%)</td>
<td>64 (94.1%)</td>
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<tr>
<td>Macrolides (mm)</td>
<td></td>
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<tr>
<td>Erythromycin</td>
<td>23.4 ± 3.8</td>
<td>2 (2.9%)</td>
<td>6 (8.8%)</td>
<td>60 (88.2%)</td>
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<tr>
<td>Glycopeptides (mm)</td>
<td></td>
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<tr>
<td>Vancomycin</td>
<td>18.9 ± 1.2</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>67 (98.5%)</td>
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<tr>
<td>Phenicols (mm)</td>
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<tr>
<td>Chloramphenicol</td>
<td>23.1 ± 2.3</td>
<td>6 (8.8%)</td>
<td>2 (2.9%)</td>
<td>60 (88.2%)</td>
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<tr>
<td>Cyclines (mm)</td>
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<tr>
<td>Tetracycline</td>
<td>19.5 ± 5.7</td>
<td>23 (33.8%)</td>
<td>10 (14.7%)</td>
<td>35 (51.5%)</td>
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<tr>
<td>Fluoroquinolones (mm)</td>
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<tr>
<td>Ofloxacin</td>
<td>18.9 ± 2.5</td>
<td>0</td>
<td>3 (4.4%)</td>
<td>65 (95.6%)</td>
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<tr>
<td>Sulfonamides (µg/mL)</td>
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<td></td>
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<tr>
<td>Sulfamethoxazole/trimethoprim</td>
<td>0.065 ± 0.079</td>
<td>0</td>
<td>0</td>
<td>68 (100%)</td>
</tr>
</tbody>
</table>

Beaton, 2019
ANTICOAGULATION / INR MONITORING

- INR monitoring at UHI, Gulu, and Mbarara sites
- Point of care testing with training of healthcare staff to adjust medication
- Currently >50 patients being actively monitored in these settings
- UHI enrollment site for INVICTUS – RCT looking at novel anticoagulation strategies in Rheumatic Atrial Fibrillation
Making active case finding more practical

Handheld echo
78% sensitive
(98% definite RHD)
87% specific
(Beaton, 2014)

Task Shifting: Non-expert users can quickly and accurately learn to screen
(Ploutz, 2015)

Intranet-based asynchronous learning with limited hands on training is effective and reproducible
(Engelman, 2017)
### CURRENT SITES OF DEDICATED RHD CARE IN UGANDA

<table>
<thead>
<tr>
<th>Site</th>
<th>Total Number Registered</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda Heart Institute</td>
<td>1488</td>
<td>~14 new cases per month</td>
</tr>
<tr>
<td>JCRC Lubowa</td>
<td>90</td>
<td></td>
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<tr>
<td>Gulu</td>
<td>491</td>
<td>~12 new cases per month</td>
</tr>
<tr>
<td>Lira</td>
<td>166</td>
<td>RHD 98; ARF 68</td>
</tr>
<tr>
<td>Mbarara</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Jinja</td>
<td>19</td>
<td>Paper registry</td>
</tr>
</tbody>
</table>
PROGRESS IN RHD CARE IN UGANDA

- 2011: Paper Registry
- 2012: Remedy Site
- 2013: Online RedCap Registry
- 2015: Regionalization of Care
- 2016: Tertiary care: Surgery or BMV
IMPACT OF REGIONALIZATION OF CARE

- RHD cases enrolled from almost every district
- Highest enrollment around regional centers – suggests access major determinant to diagnosis
- Case enrollment for region increased ($p<0.01$) each time regional center established

(Okello, 2017)
PROPORTION OF OPTIMAL BPG ADHERENCE (≥80%) RETENTION IN CARE

Legend (optimal adherence)
Green: ≥81%
Yellow: 61-80%
Orange: 41-60%
Red: ≤40%

Legend (sites)
U= UHU (Kampala)
G= Gulu
L= Lubowa
M= Mbarara

Legend (retention)
Green: ≥81%
Yellow: 61-80%
Orange: 41-60%
Red: ≤40%

Legend (sites)
U= UHU (Kampala)
G= Gulu
L= Lubowa
M= Mbarara

Longnecker et al, 2017
Number of RHD cases per site, 2013-2018

Currently >2200 Cases
Increased Uganda Heart Institute RHD Research capacity
UHI RESEARCH AND CLINICAL CARE PARTNERSHIPS
BUILDING TERTIARY CARE: VALVE SURGERY PROGRAM

• 2009: Valve surgery restarted at UHI
• Majorly limited by Costs
• ICU space limits Number of Congenital vs Adult Surgical cases
VALVE SURGERY PROGRAM

- RHD surgical camps in Past Two years
- Continue to send out cases Salam Center (Sudan) and India
- approximately 2-3 Open Heart cases per week when no visiting team
BUILDING TERTIARY CARE: BALLOON MITRAL VALVULOPLASTY

• Staff training (cath/echo guidance) at UFMG, Brazil (October, 2016)
• First independent PBMV – November 2016
• 50+ PBMV patients to date
ACCESS TO SURGERY OR BMV FOR RHD REGISTRY PATIENTS~220 SINCE 2010

Number of Surgical or BMV cases

Uganda
India
Salam Center, Sudan
Others
PROGRESS IN RHD SURGERY AND BMV AT THE UHI OVER THE YEARS
ADDRESSING INEQUITY IN RHD CARE

- Most RHD patients come from the poorest backgrounds
- UHI and Regional Centers offer Free consultations, ECG/Echo, and Government drugs for repeat follow up appoints
- BMV subsidized to as low as $300 or Free for patients in the RHD registry
- Free Surgeries during RHD surgical camps
BUILDING HUMAN RESOURCES

- 2010 UHI began to train cardiology fellows (18 trained in total)
- Invested in training abroad
- High retention; only 1 attrition
- Currently 6 adult cardiology, 5 pediatric cardiology and 4 Cardiac Anesthesia/critical care cardiology fellows

- Cardiac Catheterization (5)
- Electrophysiology (1)
- Intensive Care (1)
- Heart Failure (1)
- Cardiovascular Surgery (2)
- Cardiac ICU Nursing (5)
- Cardiac Anesthesia and Critical Care / Perfusion (3)
PATIENT SUPPORT GROUPS

ADULT SUPPORT GROUP
42 RHD patients aged 6-15 years on BPG, attending monthly peer support groups.

- Pre-post RHD knowledge assessment, a measure of health related quality of life (HRQOL) (PedsQLTM4.0), and a measure of social support (Hawthorne Friendship scale).

- Attending support groups resulted in increased total HRQOL scores.

- Increased physical functioning, social functioning and school functioning.

- Significant increases in Friendship Scale scores and RHD Knowledge scores were observed.
COMMUNITY EDUCATION

COMMUNITY SENSITIZATION

- Radio
- Posters
- Educational workshops for school teachers, health workers, Village Health Teams
COMMUNITY EDUCATION

- In Lira over 3 months for ARF study
- 503 Community members randomly sampled
- 75% listened to radio regularly
- 51.3% (n=258) had announcements on radio, and half of these could remember at least one symptom of ARF
- Only 17% (n=87) recalled from Posters
GOVERNMENT ENGAGEMENT

1. November 2017, RHDAction event in Kampala, Uganda

2. 10 member RHD National Advisory Council – sitting within the MOH (Director General of Health Services: Chair) – goal to oversee transition to a national RHD control program

3. Uganda supported WHO RHD resolution, and Dr. Omagino (director, UHI), and MOH officials travelled to Geneva to World Health Assembly, in May, 2018
ADVOCACY: INCREASING ROLE OF PATIENT SUPPORT GROUPS
EMERGING CHALLENGES: PREGNANCY IN PATIENTS POST VALVE SURGERY

- Increasing Number of Women with RHD Operated
- Low contraceptive prevalence rate
- High Societal expectations for child bearing
- Limited health workforce experience in treating patients with Artificial valves on Warfarin
NURSE LED PRIMARY CARE
### Task shifting…because of few doctors

<table>
<thead>
<tr>
<th>Profession</th>
<th>Staffing levels in Regional Referral Hospitals</th>
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<tbody>
<tr>
<td></td>
<td>Arua</td>
<td>Gulu</td>
<td>Lira</td>
<td></td>
<td></td>
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<tr>
<td>Norm</td>
<td>Filled</td>
<td>Staffing Level(%)</td>
<td>Norm</td>
<td>Filled</td>
<td>Staffing Level(%)</td>
</tr>
<tr>
<td>Doctors</td>
<td>40</td>
<td>14</td>
<td>35.0</td>
<td>36</td>
<td>12</td>
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<tr>
<td>Nurse/Midwife</td>
<td>116</td>
<td>137</td>
<td>118.1</td>
<td>169</td>
<td>125</td>
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<tr>
<td>Allied Health</td>
<td>31</td>
<td>22</td>
<td>71.0</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>187</td>
<td>172</td>
<td>192.0</td>
<td>242</td>
<td>164</td>
</tr>
</tbody>
</table>

Aliku, 2018
Understanding the Gap between ARF and RHD in Uganda

- Lira, Mulago, Mbarara, community sensitization, healthcare worker training
- (1) Fever + Joint Pain; (2) Carditis; (3) Chorea
- In Lira: 9 months, 279 children
- 64 children with definite ARF & 18 with ARF and likely pre-existing RHD
- Preliminary annual incidence data (only first 6 months, kids from Lira)
  - New ARF: 48 per 100,000
  - Including Recurrent ARF: 56 per 100,000
- Poor health seeking behavior/diagnostic capacity are major barriers
Does early detection through echo screening and initiation of secondary prophylaxis improve outcomes?

- June-August, 2018, screening of 45,000+ children (5-17) in Gulu District

916 children with borderline and mild definite RHD to be enrolled in an RCT comparing 2 year echo-outcomes for children receiving every-4-week BPG and those not receiving prophylaxis
GULU TELEMEDICINE PILOT

- Cardiologist staffing of regional referral hospitals a critical challenge
- Nurse-led clinic with daily telemedicine consultation
- Asynchronous review – 673 pts / 10 months (370 children, 55%)
- Successful image transfer in all cases
- 385 abnormal echo; RHD, n=131 (19.5%)
- Medication initiation/adjustment: 284 patients
- Disposition
  - Outpatient: 274; Admission to Gulu: 32 (8 transferred to UHI)

assessment of feasibility, acceptability, cost, and change in outcomes
CHALLENGES AHEAD
TO COVER EVERY REGION IN THE COUNTRY
Addis Ababa Communique: Recommendations FOR RHD Control In Africa

1. Establish prospective RHD registers at sentinel sites in affected member states
2. Ensure adequate supplies of high-quality benzathine penicillin
3. Guarantee universal access to reproductive health services for women with RHD and other NCDs
4. Decentralize appropriate technical expertise to the primary and district levels
5. Establish centers of excellence for cardiac surgery, which will sustainably deliver state-of-the-art surgical care,
6. Foster multi-sectoral and integrated national RHD control programmes led by the Ministry of Health,
7. Cultivate, through a strong communication framework, partnerships between the AUC
OPPORTUNITIES FOR REDUCING RHD BURDEN IN UGANDA

- School children can be empowered to report sore throat
- Over-the counter availability of antibiotics: Amoxycillin and Cotrimoxazole
- Nursing staff availability for Nurse led Care Programs
- CHWs/VHT in our Health System
- Internet connectivity and mobile phone reach + hand held echo
- Widespread radio coverage for community education on RHD
THANK YOU AND VISIT UGANDA