HEALTHY, BIRTH, GROWTH, AND DEVELOPMENT (HBGD)

LAOS NUTRITION AND COGNITION MEETING

Daniel L. Marks M.D., Ph.D.
March 16, 2016
AN INTEGRATED TEAM APPROACH TO A COMPLEX PROBLEM

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HEALTHY BIRTH, GROWTH & DEVELOPMENT

- Statement of the problem: Optimism and Opportunity
- The biology of growth stunting, wasting, and poor brain development
  - Physiology of sickness
  - Inflammation and the brain
  - Unique demands of lifecycle stages
- Pursuing the opportunities
  - Integrated package delivery
  - New tools for assessment of gestational age, growth, and cognitive development
  - HBGD knowledge integration
- *Primum non nocere* - The rise of NCDs
- Summary and Conclusions
Beyond Mortality

In 2011, it was estimated that there were 165 million stunted children < 5 years globally; estimates based on 639 national surveys from 140 countries (Black et al Lancet 2013)

Such sample surveys are usually carried out every 5 years

- Trends estimated using Bayesian hierarchical mixture models (Stevens et al, 2012)
- Do not usually include infants <3 months of age

Modeling analyses suggest that about 20% of stunting at 24 months is due to being born small for gestational age, i.e., stunting began in utero (Black et al, 2013)

- Based on 19 longitudinal studies with accurate assessment of birth length, gestational age at birth, and postnatal growth (Christian et al)
One in four children is stunted from malnutrition, limiting their physical and mental growth and locking them in poverty.

More than 40% of all kids in Tanzania are stunted.

Stunting in children under 5, 2007-2011

SOURCE: UN, data.un.org

HBGD PRIORITIZED QUESTIONS

- To what extent is growth faltering explained by pre- vs postnatal insults?
- What kind of recovery can we expect in infants born small for gestational age (sga)?
- Can we quantitatively characterize the relation and interaction between preterm birth, physical growth, and brain development?
- Are there disproportionately large contributions on growth faltering from certain pathways, and can we rank-order risk factors?
- Are there specific pathways directly impacting linear growth faltering that coincide with increased risk of noncommunicable diseases such as cardiovascular disease, obesity, and diabetes
WHAT ARE SOME CO-MORBIDITIES THAT MAY BE ASSOCIATED WITH STUNTING?

Higher risk of child mortality from infectious diseases
- Risk is magnified by underweight for height or wasting

Reduced immune development and vaccine response

Reduced cognitive function
- Age/Timing are important—youngest children are most vulnerable.
- Stunted physical growth and stunted cognitive development occur at the same stage of development and both may be influenced by similar biological and environmental risk factors (e.g., birth asphyxia; deficiencies of iodine, iron; lead exposure; low stimulation).
- The extent to which the one is a proxy for the other varies depending on the underlying factors.
UNDERLYING BIOLOGY REFLECTS ACUTE SURVIVAL CHALLENGES THROUGHOUT EVOLUTION

Predation

“Fight or Flight”
- HPA activation
- Epinephrine
- Glycolysis
- Cardiac Output
- Anesthesia
- Fear/Aggression

This response cannot be sustained.
UNDERLYING BIOLOGY REFLECTS ACUTE SURVIVAL CHALLENGES THROUGHOUT EVOLUTION

Infection

Coordinated Behavioral and Metabolic Response

This response also cannot be sustained
Starvation

- Appetite Increases
- Metabolic Rate Decreases
- Increased Foraging
- Fats are utilized for fuel
- Lean Body Mass is Spared

Sickness

- Appetite Decreases (even in a starved state)
- Metabolic Rate Elevated
- Anhedonia, Lethargy, Decreased Movement
- Wasting of Lean Body Tissues
State-Dependent Response to Nutrition

Omega-6 Fatty Acids

(Enhanced by Inflammation)
Cyclo-Oxygenases

Inflammatory Prostaglandins & Leukotrienes

Fatty Acid Oxidation
(Enhanced by Starvation)

Energy & Growth
Sickness Responses are Centrally Driven

**Inflammation**

- Anorexia
- Lethargy
- Somnolence
- Anhedonia
- Poor Sleep
- Hyperalgesia
- Neuroendocrine Disturbance
- Fever
- Sympathetic Activation
THE BRAIN IS METABOLICALLY DEMANDING

<table>
<thead>
<tr>
<th>Organ</th>
<th>REE/Kg</th>
<th>Kg</th>
<th>Total REE (Kcal/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>240</td>
<td>1.6</td>
<td>354 ± 39</td>
</tr>
<tr>
<td>Muscle</td>
<td>13</td>
<td>33</td>
<td>340 ± 104</td>
</tr>
<tr>
<td>Adipose</td>
<td>4.5</td>
<td>19</td>
<td>95 ± 48</td>
</tr>
<tr>
<td>Bone</td>
<td>2.3</td>
<td>6</td>
<td>12 ± 2.5</td>
</tr>
</tbody>
</table>

Hayes et al. Obesity Res. 10(10) 2002
To funnel energy into the immune system, the brain must decrease its energy consumption. This is especially relevant to children and infants.
THE BRAIN HAS A UNIQUE IMMUNE SYSTEM

Subramanian et al. 2014

Microbiome

Stress

Huffington Post 2015

Nutrition

- Genetics
- Epigenetics
- Resiliency
- Economics
- Politics
- Culture

Enteropathy

Toxins

Infection
INTEGRATED LIFECYCLE APPROACH TO A COMPLEX PROBLEM

Adolescent/ Preconception
- Diet & Nutrition
- Family Planning
- Immunization
- Water & Sanitation

2-5 years
- Diet & Nutrition
- Micronutrients
- Immunization
- Management of Childhood Illness
- Water & Sanitation
- Nurturing

Pregnancy
- Diet & Nutrition
- Immunization
- Health Interventions (Preeclampsia, Gestational Diabetes)
- Water & Sanitation

Preterm birth/fetal development
- Physical growth
- Neurocognitive development

0-6 months
- Breastfeeding
- Management of Childhood Illness
- Immunization
- Water & Sanitation
- Nurturing

7-24 months
- Breastfeeding
- Complementary Feeding
- Micronutrients
- Management of Childhood Illness
- Immunization
- Water & Sanitation
- Nurturing

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BRAZIL DECREASED STUNTING PREVALENCE BY 80% IN 30 YEARS

What changed?

Percentage of stunted children under five declined from 37.1% to 7.1% between 1974-2007

How?

4 factors responsible for 2/3 of the decline

- Increased access to healthcare
- Increased investment in water supply and sanitation services
- Gains in family purchasing power
- Increased maternal schooling

### OUR APPROACH AND KEY ACTIVITIES

**USING EXISTING RESEARCH AND A FOCUSED AGENDA TO ANSWER KEY QUESTIONS**

<table>
<thead>
<tr>
<th>Maximizing insights from past and ongoing studies</th>
<th>Closing knowledge gaps</th>
<th>Building a strong network</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge integration (HBGDki)</strong></td>
<td><strong>New gap filling HBGD studies</strong></td>
<td><strong>Sites</strong></td>
</tr>
<tr>
<td>• How can data from existing studies help clarify:</td>
<td>• Do we need additional studies to test impact of intervention?</td>
<td>• Can we improve our return on investment by prioritizing a smaller set of core sites?</td>
</tr>
<tr>
<td>- <strong>Lifecycle:</strong> Relative impact of prenatal and post-birth insults</td>
<td>- If so, how should we structure this study (where / when / how)?</td>
<td></td>
</tr>
</tbody>
</table>
|   - **Pathways:** Relative impact from certain pathways | • How well can we measure / predict?  
   - PTB/ fetal development  
   - Growth  
   - Neurocognitive development | |
|   - **Outcomes:** Interrelationship / interaction between the outcomes | • How can we optimize cost effectiveness of intervention packages? | |
| **Ongoing studies**                | **Measurement and tools** | **Delivery & cost effectiveness** |
| • What answers will ongoing studies provide for our overarching questions? | • Can we stratify population by risk / pathology?  
   - Nutrition (intake, quality)  
   - Gut status  
   - Metabolism | |
| • What enhancements to the studies should we make? | | |

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Primum non nocere

- Lessons from iron delivery, antenatal steroids, etc.
- Rapid weight gain after SGA produces high risk of diabetes and obesity.
- Maternal obesity is a substantial risk factor during pregnancy, and changes milk quality during lactation.
- High nutrient density, especially with low nutrient quality, produces a high risk of multiple diseases, and leads to systemic inflammation.
- Focus on local, sustainable solutions, and treasure the cultural diversity around the world.
THANK YOU
Coincidence of stunting with brain development: A window of vulnerability

**Body**

Mean anthropometric z scores from 54 countries (Victora et al., 2010)

**Brain**

Adapted from Bardin et al, *Nature*, 2012
Overall HBGD Question:
How to repeat & sustain this success elsewhere?

What intervention packages should we deliver to which group of individuals (based on underlying risk and pathologies), at what point in their life cycle? How will delivery be optimized?

Global burden of stunted children

165M

Integrated intervention package
- Nutrition
- Infection control & water access
- Nurturing

Existing interventions (Lancet, 2013)

ILLUSTRATIVE

More efficacy

How much of the burden can we solve by delivering a more comprehensive package of known interventions?

Scenario 1
How do we scale our package for cost effectiveness and deliverability?

Scenario 2
What specific factors are preventing the package from working? What changes (e.g., additional interventions) are necessary before we find the right package to scale?
MALNUTRITION AND BRAIN DEVELOPMENT
<table>
<thead>
<tr>
<th><strong>Grand Challenges Brazil:</strong></th>
<th>All Children Thriving</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grand Challenges India:</strong></td>
<td>All Children Thriving</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Grand Challenges South Africa:</strong></td>
<td>All Children Thriving</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Grand Challenges:</strong></td>
<td>Creating and Measuring Integrated Solutions for Healthy Birth, Growth, and Development</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Grand Challenges Explorations:</strong></td>
<td>Explore New Ways to Measure Brain Development and Gestational Age</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Grand Challenges Explorations:</strong></td>
<td>Explore Nutrition for Healthy Growth of Infants and Children</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Grand Challenges Brazil:</strong></td>
<td>Reducing the Burden of Preterm Birth</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Grand Challenges India:</strong></td>
<td>Healthy Growth through Agriculture and Nutrition</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Grand Challenges in Global Health:</strong></td>
<td>Achieving Healthy Growth</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Grand Challenges in Global Health:</strong></td>
<td>Preventing Preterm Birth</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Grand Challenges Canada:</strong></td>
<td>Saving Brains</td>
<td>2011</td>
</tr>
<tr>
<td><strong>Grand Challenges for Development:</strong></td>
<td>Saving Lives at Birth</td>
<td>2011</td>
</tr>
</tbody>
</table>
Grand Challenges: Healthy Birth, Growth, and Development programs

- Grand Challenges Brazil: All Children Thriving (2014)
- Grand Challenges India: All Children Thriving (2014)
- Grand Challenges South Africa: All Children Thriving (2014)
- Creating and Measuring Integrated Solutions for Healthy Birth, Growth, and Development (2014)

- Achieving Healthy Growth (2011)
- Preventing Preterm Birth (2011)
- Grand Challenges Brazil: Reducing the Burden of Preterm Birth (2013)
- Grand Challenges India: Healthy Growth through Agriculture and Nutrition (2013)

- Explore Nutrition for Healthy Growth of Infants and Children (2011)
- Explore New ways to Measure Brain Development and Gestational Age (2014)
Explore Nutrition for Healthy Growth of Infants and Children (2011)

52 Phase I projects, 6 Phase II projects:

- Use of Low Technology for Donor Breast Milk Banking (*Kiersten Israel-Ballard, PATH*)
- Generate a Mouse Model of Environmental Enteropathy (*Sean Moore, Cincinnati Children’s Hospital*)
- Improving Fetal Growth Rates in Developing Countries (*Laura Woollett, University of Cincinnati*)
- Low-cost body composition measurement for nutrition assessment (*Alistair McEwan, University of Sydney*)
- Efficient Analytical Methods for Breastmilk Micronutrients (*Lindsay Allen, USDA*)
- Biomarkers of Nutrition-Related Cognitive Development (*Clare Elwell, University College London*)

Explore New Ways to Measure Brain Development and Gestational Age (2014)

41 Phase I projects
All Children Thriving programs: Healthy Birth, Growth, and Development elements shared and unique

<table>
<thead>
<tr>
<th></th>
<th>GC Brazil</th>
<th>GC India</th>
<th>GC South Africa</th>
<th>Gates Foundation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early child development/nurturing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Preconception nutrition</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Postnatal nutrition</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Family planning</td>
<td></td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Infant sleep</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Maternal stress/ depression</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Domestic violence</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>WASH</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Conditional Cash Transfer</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Agriculture</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tbody>
</table>
COMMON FEATURES OF TRIAL DESIGN

1. Early phenotyping
2. Diagnosis
3. Stratification
4. Intervention
5. Monitoring

- **Preventive “base” intervention**
  - Nutrition, Infection control, Nurturing, Parental education

- **Therapeutic intervention**
  - Acute treatment protocols, Counseling

**GROWTH TRAJECTORY**

At baseline, deliver Preventive “base” intervention

Time (months)
<table>
<thead>
<tr>
<th>Category</th>
<th>“Must-have” tool</th>
<th>Use case</th>
<th>Investment / partner</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical growth</td>
<td>Measures of growth velocity</td>
<td>• Determine if the child is actively growing</td>
<td>Global Good, Bone plate biomarker</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Enable rapid course correction in intervention (adaptive trial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal growth / prematurity</td>
<td>Gestational age determination</td>
<td>• More accurately identify whether the fetus is growing normally and/or is at risk for PTB to assess linkages with stunting</td>
<td>GCE Phase I grants</td>
<td>2 years</td>
</tr>
<tr>
<td>Neurocognitive development</td>
<td>LMIC adapted neurocognitive development tests</td>
<td>• Assess neurocognitive development in trials in LMIC settings</td>
<td>Trial in Bangladesh, GCE RFP</td>
<td>3-5 years</td>
</tr>
<tr>
<td></td>
<td>Culturally adapted test to measure nurturing</td>
<td>• Facilitate comparison with historical data from HICs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut function</td>
<td>Gut permeability/function biomarker</td>
<td>• Assess impact of nurturing interventions on neurocognitive development in LMIC settings</td>
<td>Grand Challenges (October 2014)</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Integrated marker of inflammation</td>
<td>• Assess the impact of gut dysfunction on stunting</td>
<td>Multiple grants</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Customize intervention packages to improve gut function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Measures of nutrient intake</td>
<td>• Stratify based on risk category (anabolism vs. catabolism)</td>
<td>Grand Challenges (October 2014)</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>Validated and simple markers of exclusive breastfeeding (EBF)</td>
<td>• Asses the efficacy of interventions</td>
<td>3+ corporate partners in various stages of granting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Judge our nutrition intervention studies based on accurate, “real” intake (compliance)</td>
<td>Grand Challenges (October 2014)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stratify infants based on risk (i.e., whether they are receiving exclusive breastfeeding)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor EBF rates in our scale up efforts</td>
<td>Grand Challenges (October 2014)</td>
<td></td>
</tr>
</tbody>
</table>
MEASURED AS RECUMBENT LENGTH IN CHILDREN < 2 YEARS AND AS STANDING HEIGHT IN OLDER CHILDREN

Prone to execution error in infants!

Photo: Felicia Webb
TOOL DEVELOPMENT: A BIOASSAY FOR CHILDHOOD GROWTH

- Healthy children grow very quickly during infancy
- Our “1000 day window” does not allow for a six month interval to determine if interventions were successful
- All growth occurs exclusively at growth plates - we can develop an assay for growth plate activity
The challenge of cognitive assessment: The tension between cultural adaptation and cross-study comparisons.
New Tools for Brain Development Analysis

Eye Tracking

0-2 months

Functional Near Infrared Spectroscopy (fNIRS)


www.globalfnirs.org
Measuring Gestational Age
New Tools for Gestational Age Assessment and Risk for PTB

- Evaluation of the vaginal microbiome
- Microbiome signatures in circulation
- Fetal RNA in maternal circulation
- Fetal Hemoglobin
- Newborn lens vascularity
- Maternal and Infant Metabolomics
MISSION STATEMENT

• To facilitate collaboration, data sharing and learning from extant longitudinal clinical studies and cross-sectional databases.

• To learn from all available data rather than gaining incomplete insights from partial datasets.
INTEGRATED APPROACH FOR GLOBAL HEALTH

- NUTRITION
- VACCINES
- SANITATION
- VECTOR CONTROL

FAMILY HEALTH
90% OF THE STUNTING BURDEN LIES IN 39 COUNTRIES

Drivers of high burden in countries are not identical in space, time and geographical proximity
90% OF THE STUNTING BURDEN LIES IN 39 COUNTRIES

Drivers of high burden in countries are not identical in space, time and geographical proximity.
QUICK PEEK: WHAT DOES HBG*ki MEAN FOR HEBRAHIMA

Statistical models should:

- Disaggregate heterogeneous populations into “phenotypic” actionable sub-groups
- Scale across relevant orders of magnitude
- Quantify effect size of insults and interventions

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GIVEN CURRENT STATE HOW WELL CAN WE PREDICT HEBRAHIMA’S FUTURE STATE AT 15, 24, 60 MONTHS?

Statistical models should:
• Be predictive, permit forecasting
• Provide framework for prevention and therapeutic intervention
• Identify children at risk before faltering
PREDICTIONS CAN BE UPDATED AND WILL EVENTUALLY INCORPORATE INSULTS AND INTERVENTION RESPONSE

Prevention/Intervention ‘personalization’

- Average Causal Effect (ACE) \( E[Y_i(1) - Y_i(0)] \)
- Individual Causal Effect (ICE) \( Y_i(1) - Y_i(0) \)
AN INTEGRATED APPROACH TO A COMPLEX PROBLEM

Adolescent/ Preconception
- Diet & Nutrition
- Family Planning
- Immunization
- Water & Sanitation

2-5 years
- Diet & Nutrition
- Micronutrients
- Immunization
- Management of Childhood Illness
- Water & Sanitation
- Nurturing

Pregnancy
- Diet & Nutrition
- Immunization
- Health Interventions (Preeclampsia, Gestational Diabetes)
- Water & Sanitation

0-6 months
- Breastfeeding
- Management of Childhood Illness
- Immunization
- Water & Sanitation
- Nurturing

1-2 years
- Diet & Nutrition
- Micronutrients
- Immunization
- Management of Childhood Illness
- Water & Sanitation
- Nurturing

7-24 months
- Breastfeeding
- Complementary Feeding
- Micronutrients
- Management of Childhood Illness
- Immunization
- Water & Sanitation
- Nurturing

- Preterm birth/fetal development
- Physical growth
- Neurocognitive development

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CRITICAL QUESTIONS IN CHILD GROWTH AND DEVELOPMENT

1. **DETERMINANTS**: What are the **key determinants of stunting**, their interaction and attributable fractions?

2. **INTAKE AND ABSORPTION**: What are the **micro and macronutrients necessary for healthy growth and cognitive development**? And what factors affect their absorption?

3. **UTILIZATION & DEMAND**: How do we **optimize the utilization of nutrients**?

4. **COGNITIVE DEVELOPMENT**: What is the **linkage between stunting and impaired cognitive development** and how can we intervene on it?

5. **MARKERS & TARGETED INTERVENTIONS**: Do we have markers to **stratify stunted children** into different etiological categories to better inform **targeted interventions**?

6. **LIFE CYCLE & INTERVENTION WINDOW**: Where in the life cycle do we have the potential to **intervene with the highest impact**?

7. **MODEL OF CHILD GROWTH**: Do we understand the bioenergetics of **optimal and restricted growth**?
WE ARE ALSO USING MODELING TO LINK ANTHROPOMETRY & NEUROCOGNITIVE OUTCOMES

• Head circumference growth over gestational age **correlates with the myelination water fraction in the brain** – an indicator of early brain growth

• Our modeling efforts will **improve study design and save costs** by enabling MRIs to be conducted only **during periods of greatest head circumference and myelin growth**
BRAZIL DECREASED STUNTING PREVALENCE BY 80% IN 30 YEARS

Percentage of stunted children under five declined from 37.1% to 7.1% between 1974-2007

What changed?

- Increased access to healthcare
- Increased investment in water supply and sanitation services
- Gains in family purchasing power
- Increased maternal schooling

How?

4 factors responsible for 2/3 of the decline

- Increased access to healthcare
  - Unified Health System (1988), Family Health Strategy (1994) increased access to healthcare
  - 1996-2007: Median duration of breastfeeding increased from 7 to 14 months, duration of exclusive breastfeeding from 1.1 to 1.4 months

- Increased investment in water supply and sanitation services
  - Increased investment in public water supply and sewage systems, particularly between 1996-2007
  - 1996-2007: Percentage of poorest households with public water supply increased from 40% to 65%

- Gains in family purchasing power
  - Success of conditional cash transfer programs
  - 1996-2007: Percentage of poorest households owning a refrigerator increased from 1% to 34%

- Increased maternal schooling
  - 1996-2007: Percentage of mothers in poorest households with ≥8 years of schooling increased from 6% to 29%

PREDICTIONS BASED ON SIMILAR NEAREST-NEIGHBOR, AVATARS

Statistical models should:

- Be predictive, permit forecasting
- Provide framework for prevention and therapeutic intervention
- Identify children at risk before faltering
Functional Near Infrared Spectroscopy (fNIRS)  
An Objective Measure of Cognitive Function from Birth

0-2 months

4-8 months

9-13 months

12-16 months

18-24 months

@globalfnirs
www.globalfnirs.org