Microbiome and growth: Assessment of possible future interventions

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Birth to 2 years (z-scores)

Recommended childhood and adolescence immunization schedule, by vaccine

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Ages of administration of routine immunization services</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>At birth</td>
</tr>
<tr>
<td>OPV</td>
<td>At birth, 6wk, 10wk, and 14wk</td>
</tr>
<tr>
<td>DPT- Hib- HepB</td>
<td>6wk, 10wk and 14wk</td>
</tr>
<tr>
<td>Pneumococcal vaccine (PCV 30)</td>
<td>6wk, 10wk, and 14wk</td>
</tr>
<tr>
<td>Mumps</td>
<td>9 months</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>At birth</td>
</tr>
</tbody>
</table>
What is THE microbiome??

- Collective genomes of the bacteria, fungi, protozoa and viruses that live inside and on the human body
- About 10 times as many microbial cells as human cells
# Role of the Microbiome

<table>
<thead>
<tr>
<th>Protective functions</th>
<th>Structural functions</th>
<th>Metabolic functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen displacement</td>
<td>Barrier fortification</td>
<td>Control IEC differentiation and proliferation</td>
</tr>
<tr>
<td>Nutrient competition</td>
<td>Induction of IgA</td>
<td>Metabolize dietary carcinogens</td>
</tr>
<tr>
<td>Receptor competition</td>
<td>Apical tightening of tight junctions</td>
<td>Synthesize vitamins e.g., biotin, folate</td>
</tr>
<tr>
<td>Production of anti-microbial factors e.g., bacteriocins, lactic acids</td>
<td>Immune system development</td>
<td>Ferment non-digestible dietary residue and endogenous epithelial-derived mucus</td>
</tr>
</tbody>
</table>

Commensal bacteria

**IgA**

- Short-chain fatty acids
- Mg$^{2+}$
- Ca$^{2+}$
- Fe$^{2+}$
- Vitamin K
- Biotin
- Folate

**EMBO reports (2006) 7, 688–693. doi:10.1038/sj.embor.7400731**
Microbiome composition (Maturity) is strongly associated with age.

Science (New York, N.Y.) 339: 548-54
Bangladesh Microbiota study

• WHZ was associated with relative microbiome immaturity among children with moderate acute malnutrition.

Bangladesh Microbiota study
Malnutrition was only partly and briefly reduced following nutritional intervention

Longitudinal comparative study of fecal microbiomes of twin pairs in Malawi who became discordant for kwashiorkor.

Allowed control for genetic factors and common environmental and diet exposures.

Before, during, and after treatment with Ready-to-use therapeutic food.

Sick twin: lack of progression towards ‘older gut microbiome’ structure.
Malawi twin study

- Microbiota composition differs between twins discordant for kwashiorkor
- Fecal transplants from children with kwashiorkor caused severe malnourishment in mice, regardless of diet

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ONE HOUSE/ONE HEALTH

A new lens on child growth & development

Pregnant Women & Mothers

Shared Microbiome

Children under 5 yrs.

Asset Accumulation

Protein Allocation

Pathogen Transmission

↑ Maternal Mortality
↑ Morbidity (other infections)
Low Birthweight infants
Poor Nutrition

↑ Mortality
↑ Morbidity (other infections)
Stunting, wasting, malnutrition
Cognitive delay
Focus on prevention at household level (Humans+Animals=Household)

• Once established, effects of malnutrition hard to reverse
  – Relapse rates high: ~100% if returned to same nutritional environment
  – Physical & cognitive damage permanent
  – Infection & “environmental enteric dysfunction (EED)” play key roles

• No single treatment effective; multifactorial approach required
  – Complex synergy of recurrent pathogen exposure, inadequate nutrition, & enteric disease
  – Intergenerational factors include maternal malnutrition & influence on infant microbiome
PHASE 1

Are the microbiomes of children, cows, chickens, and the environment shared within a household?

Is microbiome sharing related to malnutrition?

Is child illness related to sharing microbiomes between children, cows, chickens, and the environment?

PHASE 2:

Could an intervention with animals result in resetting of the human microbiome?
Linked Animal and Human Surveillance

• Syndromic Surveillance Project, Kisumu, Kenya
  • Allen School Collaboration with CDC-KEMRI
  • Identification of known and unknown causes of diseases
  • Econometric impact assessment
Samples

- Chicken Cloacal swab
- Cow Manure sample
- Child Stool sample
- House surface Swab
**Work Flow**

1. **Manure**
2. **Extract DNA**
3. **Test DNA quality**
4. **Ship DNA to Washington**
5. **PCR of 16s rRNA gene**
6. **Sequence DNA**
7. **Align sequences**
8. **Analyze data**
9. **Report back and share knowledge**
10. **Test DNA quality**
Randomize

Baseline assessment

**ARM 1**
Standard of Care (WASH + nutritional interventions where indicated)

**ARM 2**
Standard of Care PLUS Abx to Moderate/Severely malnourished U5s

**ARM 3**
One House/One Health Standard of Care + Abx to all U5s PLUS fecal transplant in all household animals

Mortality (total, U5, maternal)
Morbidity (self-report, hospitalization)
Birth outcomes (birth weight, survival)
U5 growth & Development
U5 enteric function (L/M ratio)*
Microbiome Evaluation (humans and animals)*
Pathogen Carriage (pneumococcus, *Salmonella* spp. etc.)*
Antibiotic resistance (commensal E. coli and pathogens)*
Animal health and survival
Economic productivity and expenditure

*To be performed in a subset of all households
Azithromycin to prevent post-discharge morbidity and mortality

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Background

- 3.5 million children < 5 years die each year in sub-Saharan Africa
- 70% of these deaths are attributed to infectious causes
- Children admitted to and subsequently discharged from hospital are a high-risk/accessible population
- “Post-discharge syndrome”

Kilifi Kenya

Community:
- 3.9 deaths per 1000 children
- Post discharge*:
  - 38 deaths per 1000 children

* 1st admission

Liu, 2012; Weins, 2013; Moisi, 2011
Randomization & Follow up

RCT
Enrolled
1400 children
Discharged from hospital following admission for non-traumatic condition

Treatment Arm
700 Children
Randomized to azithromycin 10mg/kg/day X 1 day, then 5mg/kg/day X 4 days
1st dose directly observed

Placebo Arm
700 Children
Randomized to placebo X 5 days, 1st dose directly observed

Enteric Function Cohort
150 Children
Treatment arm

Contact Cohort
150 Primary Caregivers of children in treatment arm of the enteric function cohort
AST testing of isolated S. pneumonia and E.coli

200 Children
AST testing of isolated S. pneumonia and E.coli

90-Day Follow Up

200 Children
AST testing of isolated S. pneumonia and E.coli

6-Month Follow Up

Enteric Function Cohort
150 Children
Placebo arm

Contact Cohort
150 Primary Caregivers of children in treatment arm of the enteric function cohort
AST testing of isolated S. pneumonia and E.coli
Summary

• The microbiome appears to be associated with healthy growth
• We don’t know how to fundamentally reshape the microbiome to drive health
• Sharing of the microbiome may present a potential opportunity for intervention
• Tremendous uncertainty, Unbelievable opportunity
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